W.-T. Chiu, M.-C. Kao, C.-C. Hung,
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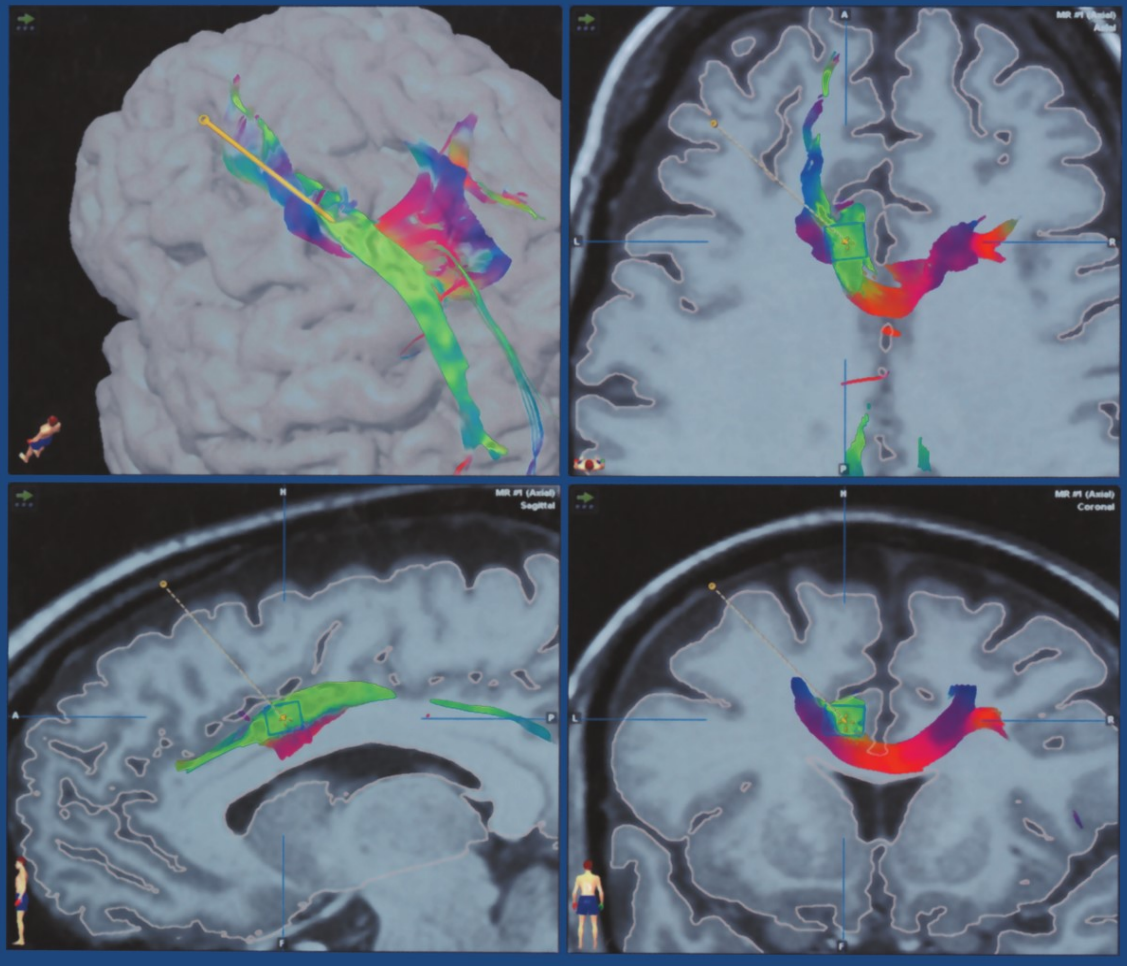
B. Hoffer, Y.-H. Chiang
Editors

Reconstructive Neurosurgery



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Acta Neurochirurgica
Supplements

Editor: H.-J. Steiger

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Acta Neurochirurgica
Supplement 101

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Prof. Dr. Wen-Ta Chiu
Department of Neurosurgery, Municipal Wan Fang Hospital,
Taipei Medical University, Taipei, Taiwan, R.O.C.

Prof. Dr. Yung-Hsiao Chiang
Department of Neurosurgery, Taipei Medical University Hospital,
Taipei Medical University, Taipei, Taiwan, R.O.C.

Prof. Dr. Ming-Chien Kao
Prof. Dr. Ching-Chang Hung
Department of Neurosurgery, National Taiwan University Hospital,
National Taiwan University, Taipei, Taiwan, R.O.C.

Prof. Dr. Shinn-Zong Lin
Center for Neuropsychiatry, China Medical University Hospital,
China Medical University, Taichung, Taiwan, R.O.C.

Prof. Dr. Han-Jung Chen
Department of Neurosurgery, E-Da Hospital, I-Shou University, Kaohsiung, Taiwan, R.O.C.

Prof. Dr. Simon F. T. Tang
Department of Rehabilitation Medicine, Chang Gung Memorial Hospital,
Chang Gung University, Taipei, Taiwan, R.O.C.

Prof. Dr. Barry J. Hoffer
National Institute on Drug Abuse, National Institute of Health, Baltimore, USA

Printed in Austria
SpringerWienNewYork is a part of Springer Science + Business Media
springer.at

Typesetting: Thomson Press, Chennai, India
Printing and Binding: Druckerei Theiss GmbH, St. Stefan, Austria, www.theiss.at

Printed on acid-free and chlorine-free bleached paper

SPIN: 12110100

Library of Congress Control Number: 2008924786

With 52 Figures (thereof 3 coloured)

ISSN 0065-1419
ISBN 978-3-211-78204-0 SpringerWienNewYork

Acta Neurochir Suppl (2008) 101: V–VI

Printed in Austria

Preface

Neurosurgery treatment is being transformed towards functional recovery, which is the goal of "Reconstructive Neurosurgery". Initially electro-stimulation was applied to modulate disrupted central nervous system function. More recently, new frontiers use modern technology to reconstruct the vascular tree by stenting stenotic vessels, to regenerate diseased neurons by transplanting stem cells, to reconnect injured peripheral nerves by applying growth factors and to provide better treatments for traumatic brain injury patients by designing new assessment tools and strategies.

A number of these advancements were presented at the 5th Scientific Meeting of the Neurorehabilitation and Reconstructive Neurosurgery Committee of the World Federation of Neurosurgical Societies (WFNS), in conjunction with the 2nd Congress of the International Society of Reconstructive Neurosurgery (ISRN) which was held in Taipei are included in this volume to document the current state of the art in reconstructive neurosurgery.

This volume presents advances in reconstructive neurosurgery focusing on the fields of neurotrauma and neurodegenerative disorders. The highlights include: building an international strategy for risk reduction, documenting a multidisciplinary approach towards restoration of function in paraplegic spinal cord-injured patients, describing a new approach for statistical analysis in traumatic brain injury trials, describing blood flow changes in diffuse brain injury, discussing rehabilitation programs in Germany following acute brain injury, describing research data from Taiwan on neurotrauma, showing the neuropsychiatric effects from deep brain stimulation for movement disorders, defining the role played by imaging for deep brain stimulation targeting in mental illness, using radiosurgery in treatment of trigeminal neuralgia comparing noninvasive treatment versus microvascular decompression in the treatment of trigeminal neuralgia, describing the development of radiosurgery from brain to the spine, listing new transgenic animal models of Parkinson's disease, discussing gene therapy for neuropathic pain and Parkinson's disease, and finally, discussing constrained-induced movement therapy for stroke patients, and endovascular therapy for cerebrovenous disorders. These articles provide an updated comprehension of reconstructive and rehabilitative neurosurgery.

Wen-Ta Chiu, MD, PhD,
Vice-President and Professor,
Taipei Medical University,
President, Taiwan Neurotrauma Society,
President, Academy for Multidisciplinary
Neurotraumatology (AMN)

Yung-Hsiao Chiang, MD, PhD,
Chairman, Department of Neurosurgery,
Taipei Medical University Hospital,
Associate Professor, Taipei Medical University

Acknowledgements

We sincerely appreciate those people who provided useful and helpful contribution to this book. Without their assistance and consideration, this book would not be ready for publication.

First of all, we would like to thank all the editors, for their dedication and effort to do the editing work. They are Wen-Ta Chiu, Barry Hoffer, Ching-Chang Hung, Ming-Chien Kao, Simon Tang, Shinn-Zong Lin, Han-Jung Chen, and Yung-Hsiao Chiang.

Secondly, we would like to thank the Executive Committee of International Society of Reconstructive Neurosurgery who demonstrated their great interest in publishing this book. The Committee members are Yoichi Katayama (*Japan*), Jin Woo Chang (*Korea*), Han-Jung

Chen (*Taiwan*), Wen-Ta Chiu (*Taiwan*), Zhang-Jian Guo (*China*), Maximilian Mehdorn (*Germany*), Carlo Pagni (*Italy*), Wai S. Poon (*China*), Ali R. Rezai (*USA*), Bomin Sun (*China*), Massimiliano Visocchi (*Italy*), Klaus von Wild (*Germany*) and Takamitsu Yamamoto (*Japan*).

Thirdly, we are grateful to the support from Taiwan Neurotrauma Society, Taiwan Neurosurgical Society, International Cooperation and Development Fund (Taiwan), The Injury Prevention and Disaster Medicine Research Foundation, Wan Fang Hospital, Taipei Medical University Hospital and Taipei Medical University.

Finally, we thank Ms. Shu-Fen Chu, Wan-Chen Tsai and Celine Wang for their assistance in preparation of the manuscripts.

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Printed in Austria

The role of modern imaging modalities on deep brain stimulation targeting for mental illness

M. Sedrak[1], A. Gorgulho[1], A. F. De Salles[1], A. Frew[2], E. Behnke[1], W. Ishida[1], T. Klochkov[1], D. Malkasian[1]

[1] Division of Neurosurgery, David Geffen School of Medicine, University of California Los Angeles (UCLA), Los Angeles, CA, USA
[2] Department of Radiology, David Geffen School of Medicine, University of California Los Angeles (UCLA), Los Angeles, CA, USA

Summary

Introduction. The reversible nature of deep brain stimulation (DBS) brought renewed interest on surgery to medically intractable mental illnesses. The explosion of anatomical and functional imaging has allowed the development of new potential targets and the understanding of historical targets.

Methods. Fifteen patients undergoing stereotactic surgery for movement disorders, at UCLAs interventional MRI operating-room, were studied with fiber tracking. Stereotactic targets and fiber tracking were determined on MRIs using the Schaltenbrand-Wahren atlas for definition in the iPlan software. Cingulate, subcaudate, BA25/CgWM, amygdala, posterior hypothalamus, orbitofrontal cortex, nucleus accumbens, anterior limb of the internal capsule and dorsomedial thalamus were studied. DTI parameters used ranged from 10 to 20 mm for voxel size in the x/y/z planes, fiber length was kept constant at 36 mm, and fractional anisotropy (FA) threshold varied from 0.20 to 0.25.

Results. Reliable interconnectivity of targets were determined with DTI and related to PET imaging. Mental illness targets were observed with functional and fiber tract maps. This confirmation yields reliability to DTI imaging in order to determine novel targets and enhance the understanding of areas not well understood.

Conclusions. Currently available imaging techniques, the reversibility of DBS to modulate targets promises to bring a brighter future for surgery of mental illness.

Keywords: DTI; MRI; OCD; depression; diffusion tractography; mental illness; PET; psychosurgery.

Introduction

Since the beginning of psychosurgery applications in humans in the 1930s, there has been controversy [18]. Although Egas Moniz was suggested to be nominated for the 1944 Nobel Prize by Walter Freeman for "his fundamental contribution to the surgical treatment of functional mental disorders," little understanding was known regarding mental illness [18]. By the 1950s, stereotactic surgery for movement disorders became commonplace along with several psychosurgery applications [23]. Ablative techniques were abandoned for behavior surgery following the controversies of psychosurgery. Deep brain stimulation brings new hope for behavior surgery as it is reversible and adjustable. Furthermore, the knowledge and fundamental understanding of the brain has rekindled hopes for treating mental illness refractory to medical therapy.

Functional imaging modalities, such as PET and fMRI have demonstrated various abnormalities in obsessive-compulsive disorder, major depression, Tourette syndrome, cluster headache, and numerous other disorders. As these modalities have added to our understanding of disease states, understanding fundamental brain interconnectivity will greatly enhance our interpretation and ultimate understanding of the brain in its disease states.

The application of Diffusion Tensor Magnetic Resonance Imaging has enhanced the ability to view anatomical detail beyond what is seen by conventional MRI or CT scans. This diffusion tensor imaging (DTI) observes the net diffusion of water along fiber tracts allowing visualization of their orientation in space [4]. Because of this fractional anisotropy (FA), visualization along unimpeded fibers tracts is optimal, but the resolution of intersecting bands of fibers is limited. Despite this clear limitation to the technique, DTI imaging has greatly surpassed any other immediately available imaging modality with regards to the anatomical visualization of fiber tracts *in vivo*.

In this preliminary study, we sought to identify major fiber tract bundles by DTI as they relate to the anterior

Correspondence: Antonio A. F. De Salles, M.D., Ph.D., Department of Neurosurgery, David Geffen School of Medicine, University of California Los Angeles, 10949 Leconte Avenue, Suite 2120, Los Angeles, CA, USA. e-mail: adesalles@mednet.ucla.edu

cingulate gyrus, nucleus accumbens, subcaudate region, BA25/CgWM, amygdala, posterior hypothalamus, inferior thalamic peduncle, anterior limb of the internal capsule, and dorsomedial thalamus. These targets have both historical significance as well as modern implications for deep brain stimulation and neurosurgical interventions.

Materials and methods

After institutional review board (IRB) approval, we retrospectively reviewed 15 MRIs of patients who underwent DBS for movement disorders (Table 1). These patients had DTI imaging pre-operatively performed in 1.5 Tesla Sonata intraoperative MRI (iMRI) suite at UCLA Medical Center. Fiber tracking acquisition was undertaken before placement of the leksell stereotactic frame, placed parallel to Reid's line under propofol sedation. A detailed description of the stereotactic procedure as well as the imaging acquisition for targeting has been previously reported. [5, 12].

Anterior cingulate, nucleus accumbens, subcaudate region, BA25/CgWM, amygdala, posterior hypothalamus, inferior thalamic peduncle, anterior limb of the internal capsule, and dorsomedial thalamus targets were identified by stereotactic coordinate targeting utilizing the Schaltenbrand-Wahren atlas for definition and confirmation in the iPlan software (BrainLab, Heimstetten, Germany). Volume of interest (VOI) was defined at the region of interest (ROI) along the factitious trajectory for DBS planning. Fiber tractography was performed at each seed point in the VOI. DTI parameters used ranged from 10 to 20 mm for voxel size in the x, y and z-plane, minimal fiber length was kept constant at 36 mm, and fractional anisotropy (FA) threshold varied from 0.20 to 0.25.

Table 1. *Demographic characteristics of the patients with DTI MRI analyzed for mental illness targets. PD, Parkinson disease; CP, Cerebral Palsy; STN, Subthalamic Nucleus; GPi, Globus Pallidus Internus*

Diagnosis	Age	Sex	Target
PD	79	M	STN bilaterally
PD	62	F	GPi bilaterally
PD	75	M	STN bilaterally
PD	66	M	STN (right)
PD	71	F	STN (left)
CP with dystonia	15	F	GPi bilaterally
CP with dystonia	21	F	GPi bilaterally
PD	45	M	STN bilaterally
PD	55	F	STN bilaterally
CP with choreoathetosis	29	F	GPi bilaterally
PD	52	M	STN bilaterally
PD	45	M	STN bilaterally
PD	48	F	GPi bilaterally
PD	61	M	STN bilaterally
PD	54	M	STN bilaterally

Results

Anterior cingulate coordinates calculated to 7 mm lateral to midline and 20 mm caudal to the tip of frontal horns of the lateral ventricle and 29 mm dorsal to the AC–PC plane located in the center of the cingulate gyrus white matter. DTI imaging at this target demonstrated fibers in the cingulate fasciculus as well as fibers directed towards prefrontal regions. Fibers of the corpus callosum were in close proximity and also incorporated (Fig. 1).

Nucleus accumbens coordinates calculated to 7 mm lateral to midline, 4 mm ventral to AC–PC plane, and 1.5 mm rostral to anterior edge of anterior commissure. DTI imaging at this target demonstrated several groups of fiber bundles directed towards orbitofrontal/prefrontal areas, via uncinate fasciculus to temporal lobe, towards tegmentum of midbrain/pons, the fornix, and the inferior occipito-frontal fasciculus (Fig. 2).

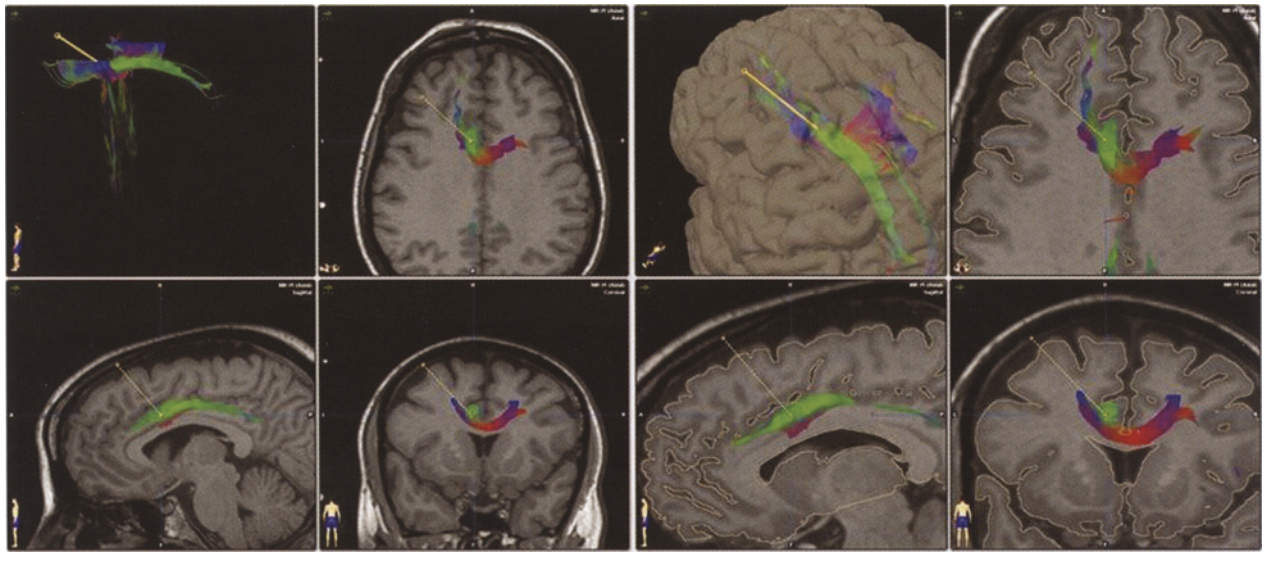

Fig. 1. DTI processing at anterior cingulate target. Fibers are seen in the cingulate fasciculus as well as fibers directed towards prefrontal regions

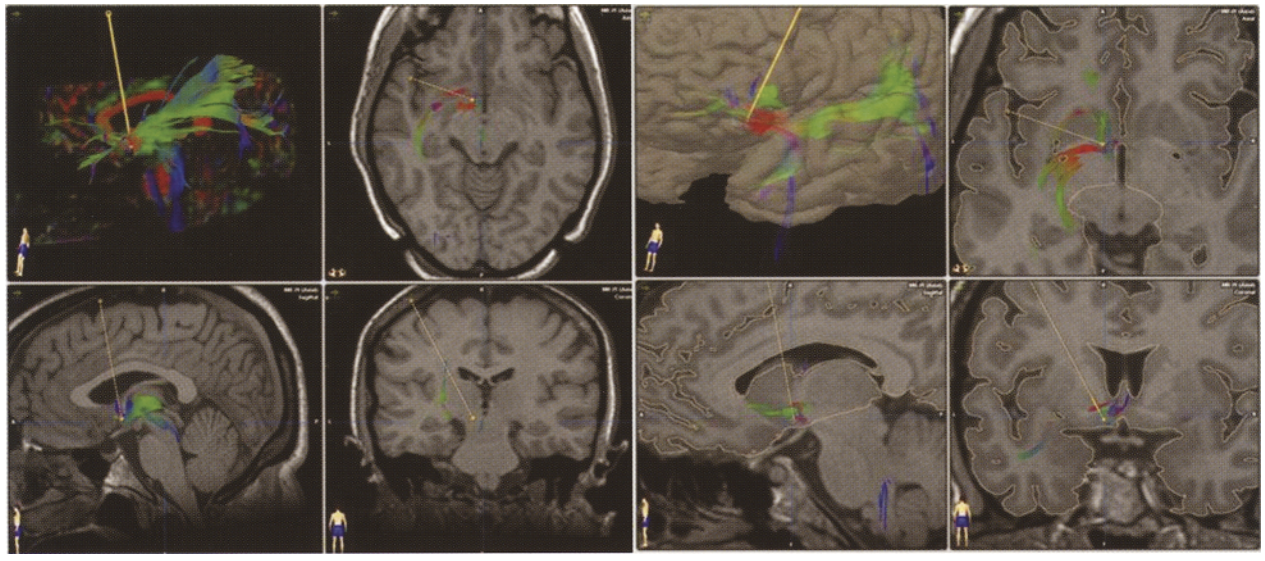

Fig. 2. DTI processing at nucleus accumbens. Fiber tracts can be seen directed towards orbitofrontal region, brainstem tegmentum, temporal lobe, the fornix, and through the inferior occipito-frontal fasciculus

Subcaudate region coordinates calculated to 15 mm lateral to midline and 11 mm above the planum sphenoidale at the most anterior part of the sella turcica. This was 19 mm anterior to the anterior commissure, 15.5 mm lateral to midline, and 10.5 mm ventral to AC–PC plane. DTI fibers could be seen directed towards orbitofrontal areas and posteriorly through the inferior occipito-frontal fasciculus.

BA25/CgWM coordinates calculated to 6 mm lateral to midline, 2 mm ventral to AC–PC plane, and was 3 mm caudal to the tip of the frontal horn. This was 24 mm anterior to anterior commissure, 6 mm lateral to midline, and 2 mm ventral to AC–PC plane. DTI imaging revealed fibers directed towards orbitofrontal/prefrontal regions as well as to cingulate fasciculus (Fig. 3).

Posterior hypothalamus coordinates calculated to 3 mm lateral to midline, 3 mm rostral to midcommissural point, and 5 mm ventral to AC–PC plane. DTI map shows numerous connections. Namely, projections into orbitofrontal regions, prefrontal regions, fornix, and tegmentum of brainstem could be seen.

Inferior thalamic peduncle coordinates calculated to 8 mm caudal to the anterior commissure, 6 mm lateral to midline, and at the level of the AC–PC plane. DTI

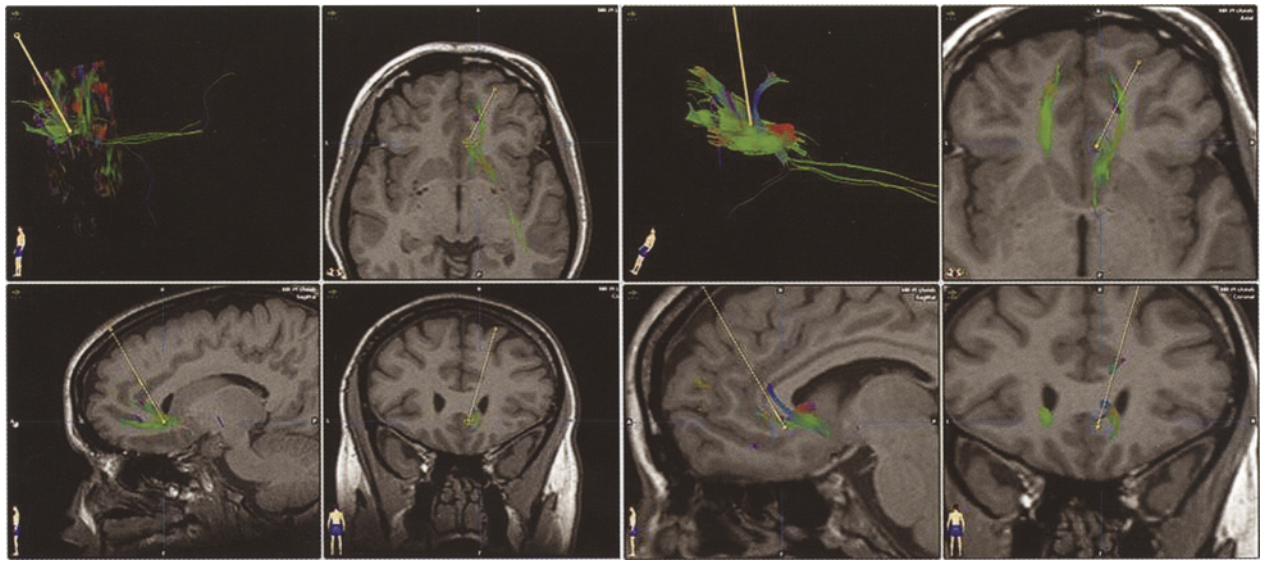

Fig. 3. DTI imaging at BA25/CgWM. Fibers can be seen directed towards prefrontal and orbitofrontal regions as well as to the anterior cingulate

imaging showed connections to thalamus, tegmentum of brainstem, and prefrontal regions. Anterior limb of the internal capsule coordinates calculated to 20 mm lateral to midline, 7 mm caudal from the tip of the frontal horn, and was at the level of the AC–PC plane. Fiber bundles were observed projecting towards orbitofrontal and prefrontal regions, via uncinate fasciculus to temporal lobe, as well as to parietal and occipital lobes.

Dorsomedial thalamus coordinates calculated to 5.8 mm lateral to midline, 14.8 mm dorsal to the AC–PC line at the midcommissural point. DTI imaging showed heavy fiber bundles directed towards the prefrontal region through the superior thalamic peduncle. The fornix was also in close proximity and fibers could be seen heading to the temporal lobe.

Coordinates for the amygdala were 18.8 mm lateral to midline, 14 mm ventral to AC–PC plane, and 1 mm caudal to the anterior commissure. When the amygdala was targeted, the DTI map showed fibers projecting through the uncinate fasciculus to the hypothalamic and septal regions as well as fibers passing through the tegmentum of the brainstem. The region of the inferior occipito-frontal fasciculus was incorporated and also the optic radiations. Coordinates for the hippocampus were 18 mm lateral to midline, 17 mm ventral to AC–PC plane, and 7 mm posterior to anterior commissure. When the hippocampus was targeted, the DTI maps showed fibers projecting through the fornices. In addition, the uncinate fasciculus was also seen as well as fibers of the optic radiations and the inferior occipito-frontal fasciculus. There were many fiber tracts overlapping between the amygdala and hippocampal targets.

Discussion

As the demand for neurosurgical treatment of mental illnesses continues to rise, enhanced anatomical and functional imaging will be required to match this demand. DTI imaging clearly enhances our interpretation of functional imaging, providing new insights, understanding, and targets that may be utilized for the treatment of various diseases.

We explored many of the regional connections both within and surrounding critical structures involved in mental illness with DTI imaging. Clearly, regions known to be involved in mental illness were identified and fibers emanating from these regions, projecting to other brain structures involved with mental illness were visualized. For example, many of the connections we found between the amygdala and hippocampus regions are similar to results found in the literature [21]. Hippocampal and amygdaloid interactions with nucleus accumbens have been well identified [9]. In our DTI analysis, we could see that the closest fiber tract emanating from that region was contained in the uncinate fasciculus.

DTI images of the uncinate fasciculus, inferior occipito-frontal fasciculus, and optic radiations seen in our study coincides with other DTI studies [10]. In addition, many of the prefrontal and orbitofrontal connections seen has marked agreement with known frontal lobe anatomy [24]. The prefrontal cortex has numerous parallel circuits and mediate diverse behaviors and emotions [3]. The prefrontal region in our study demonstrated numerous connections and tracts in relation to the anterior cingulate gyrus, nucleus accumbens, anterior limb of the internal capsule, dorsomedial thalamus, posterior hypothalamus, and BA25/CgWM.

There has been a boost of neuroimaging studies attempting to define anatomical and/or functional patterns of abnormalities correlating to defined psychiatric disorders. Many of the evidences are not clear cut. It is not uncommon that opposite findings are reported by different studies in regards to volumetric changes in brain structures [6, 17, 19, 26] and PET findings [1, 2]. These new imaging modalities allowed however substantial advance in neuroanatomical and functional knowledge about intrinsic abnormalities specific linked to the major psychiatric disorders [27]. For instance, functional disruption of the normal dopaminergic innervation involving the caudate, putamen, amygdala, midbrain and ventral striatum in schizophrenic patients has been consistently reported in the literature [13, 15, 16]. Synthesis and dopamine turnover was elevated about 20% in the caudate and the putamen and about 50% in the amygdala and the midbrain of patients with schizophrenia [11]. borderline personality disorder, characterized by uncontrolled anger often leading to aggressiveness, showed consistent hypoactivation of the pre-frontal cortex (PFC) and ventral amygdala circuitry mediated by serotonin[17] [20]. In fact it appears to be a disconnection between ventral amygdala and Brodmann areas 11, 12 and 47 in the PFC on the right side of borderline personality disorder patients [17]. This circuitry is well known to be involved in anger response and handling of negative emotions [7, 8, 22]. Obsessive compulsive disorder patients presented hyperactivity at the medial and ventral frontal cortex encompassing anterior cingulated area and basal ganglia with evidence of decreased NAA concentrations in the anterior cingulated area [25]. Major depression patients consistently have shown increased

cerebral blood flow (CBF) measured by PET in the subgenual cingulate area (BA 25) and decreased metabolic activity in the pre-frontal cortex (BA 9/46), premotor (BA6), dorsal anterior cingulate (BA 24) and anterior insula [14].

The areas described as relevant to define a disease pattern were evaluated in our study and we were able to confirm the identification of these pathways in patients with normal anatomy and function, which is an important step validating the DTI modality for patients with mental disorders. In this preliminary study using DTI imaging to embrace various fiber territories, we can further understand the implications of mental illness targeting for deep brain stimulation. Clearly, a comprehensive anatomical and functional analysis is beyond the scope of this article. Tracts in direct connection to, or in close association with, various targets can be identified. Furthermore, as our knowledge of deep brain stimulation and mental illnesses grows other targets, such as fiber bundles, may be identified and utilized.

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Neurorehabilitation

Acta Neurochir Suppl (2008) 101: 9–12

Printed in Austria

Deep brain stimulation for movement disorders and its neuropsychological implications

H. M. Mehdorn[1], S. Goebel[1], D. Falk[1], J. Volkmann[2], B. Leplow[3], M. O. Pinsker[1]

[1] Department of Neurosurgery, University Clinics of Schleswig-Holstein Kiel, Kiel, Germany
[2] Department of Neurology, University Clinics of Schleswig-Holstein Kiel, Kiel, Germany
[3] Institute of Psychology, University of Halle, Halle, Germany

Summary

Deep brain stimulation (DBS) has gained increasing attention as a therapy for movement disorders. Neuropsychological alterations can accompany the disease evolution and medical therapy of PD. Also, interfering abruptly with the biological balance by means of a surgical intervention into complex circuits with motor but also cognitive and limbic functions, could potentially cause severe problems. Because cognitive or emotional impairments may have an even stronger impact on quality of life, than motor symptoms, care must be taken to perform surgery in the safest possible way to exclude adverse effects in these domains.

Detailed neuropsychological evaluations may become helpful to further understand the mechanisms underlying some aspects of the clinical pictures both pre- and postoperatively and to define risk populations, that should be excluded from this intervention.

Keywords: Deep brain stimulation; movement disorders; neuropsychological alterations; dementia; depression.

Introduction

Deep brain stimulation has gained increasing attention over the last years particularly for treatment of movement disorders, but also other diseases could potentially be treated with DBS, particularly neuropsychiatric disorders.

A well known part of the natural history of PD is mental deterioration. Cognitive deficits are observed very frequently in Parkinson's disease (PD): in some studies, more than 90% of the patients were impaired compared to matched normal controls [25]. The cognitive changes are an important predictor for quality of life [28].

Correspondence: H. Maximilian Mehdorn, M.D., Ph.D., Department of Neurosurgery, University Clinics of Schleswig-Holstein Campus Kiel Schittenhelmstr. 10 D – 24105 Kiel, Germany.
e-mail: mehdorn@nch.uni-kiel.de

Between 15 and 20% of PD patients develop a frank dementia [1]. However, also less severe cognitive impairment is a well recognized feature of the disease. Cognitive deficits may be prominent even in early stages of the disease [22] and were actually found in first-degree relatives without PD [13].

PD patients without dementia predominantly exhibit impairments in executive functions. Executive functions are higher-level cognitive processes involved in cognitive control and are mainly executed by the frontal lobes [15]. Impairments in cognitive functions tend to show up globally, affecting all aspects of cognition and behaviour.

The underlying pathology lies within the disturbances of the frontal-subcortical circuits due to the loss of dopaminergic cells within the substantia nigra [2, 6, 20]. Fronto-striatal circuits connect the frontal lobes with the basal ganglia and mediate not only motor, but also cognitive and behavioural programs.

It is obvious that neuropsychological alterations of potential candidates may have an impact on the outcome of surgical interventions. Although they aim at the basal ganglia with the intention to improve motor functions they may affect these delicate circuits resulting in alterations of neuropsychological or even neuropsychiatric importance. These interferences may become important from a surgical point of view in three regards:

1. patient selection for surgery
2. acute side effects during surgery
3. outcome following surgery

These aspects will be discussed on the basis of our own experience as well as those of others (More extensive review s. 23).

Table 1. *Patients treated with DBS from January 1999 to June 2007 at Kiel*

Underlying disease	Total number of patients	Mean age of patients (years)
PD	234	59.8
Dystonia	52	43.5
Essential tremor	23	67.3
ED-related tremor	27	38.5
Cluster headache	2	43.0
Others	15	58.0

Material and methods

In our centre we have, between January 1999 and June 2007, performed 353 DBS operations on patients with a variety of disorders which are listed in Table 1.

Our centre has initiated and participated in a series of multi-centre studies investigating the benefits and risks of DBS in order to clarify its role for various conditions (e.g., improvement of PD due to DBS compared to best medical treatment or stimulation related improvement in dystonic patients compared to those with sham stimulation).

The indications for DBS in PD were those commonly agreed upon. Surgical techniques may vary slightly from site to site, our techniques have also been described in detail [21]. From a neuropsychological point of view it is important to note that patients with dementia or those thought unable to actively cooperate during the procedure are excluded from surgery since the major part of DBS in PD is performed under local anaesthesia.

Neuropsychological evaluation before and after the operation includes Mini Mental score, Mattis dementia rating and if possible additional tests. The patients are followed as outpatients in a regular fashion and are re-admitted to our centre e.g., for exchange of the pulse generators.

Results

Patient selection for surgery

From all patients admitted to our centre for possible DBS, approx. only 10% are considered candidates for DBS and eventually undergo the procedure. A variety of reasons account for this low number of surgical candidates: a majority is thought to be not sufficiently well treated medically, i.e., medical therapy could be optimized; approx. 20% are thought to have contraindications against surgery because of poor mental status – often presenting with a MRI scan presenting cerebral atrophy to such a degree that placement of DBS electrodes is considered to harbour extensive risk of cortical vessel injury or ventricular passage by the electrodes.

Acute side effects during and after surgery

Depending on the site of microelectrode placement into the subthalamic nucleus resp. its vicinity a variety of unwanted symptoms can be provoked: mania, euphoria and laughter when the posterior dorsal part of the STN is stimulated [18] and hypomania up to depression and anxiety [3] when the substantia nigra is stimulated. Using multi-trajectory microelectrode recordings (MER) and test-stimulation with up to five electrodes, to delineate the borders of the STN, we have observed only in one single patient such a side effect as unexplained happiness and laughter as well as tears.

Our group [32] studied the acute effects of DBS to the STN vs. a single L-Dopa dose upon symptoms of depression and hedonic tone and observed that, while depressive symptoms improved to the same extent under both therapies, hedonic tone improved only with L-dopa.

Outcome following surgery

Few larger studies have been concerned about neuropsychological alterations. Mallet *et al.* [19] stimulated the ventral posterior (limbic) part of the STN and were able to alleviate symptoms of obsessive compulsive disorder (OCD), in addition to symptoms of PD in 2 patients. On the other hand, Dujardin *et al.* [11] studied patients who had undergone DBS to the STN and found reduced emotional facial expression decoding capacities. They postulated that such restrictions might influence later social life.

Schneider *et al.* [27] have shown that DBS of the STN enhances emotional processing in PD patients which is in contrast to the findings of Dujardin *et al.* [11]. Also conflicting data are published with regards to the development of cognitive functions which were found to decline [29] while others had seen no alterations over time [8, 16]. The recently published multicentre study on STN DBS [9] particularly studied the benefit concerning quality of life. Highly significant improvement was noted in the surgical group concerning the parameters which constitutes PDQ-39, i.e., mobility, activities of daily living, emotional well-being and stigma, while significant improvement was noted concerning bodily discomfort. On the other hand it needs to be noted that one patient in the surgical group committed suicide 5 months after DBS while a patient in the medically treated group died from a car accident which he had provoked during a psychotic episode. Also, transient symptoms of depression were noted in two surgical patients and in eight medical patients. Patients who had undergone DBS from our centre within the framework of this study were evaluated closely by Mattis dementia scale, and there was no statistical difference for a follow-up period of 6 months.

Discussion

Patient selection for DBS on the basis of neuropsychological considerations alone is certainly not the standard today; however, these considerations need to be taken into account seriously since, as Perriol *et al.* [24] state, the current implantation procedure does not fully take into account the functional heterogeneity within the target. There are, however differences between various targets: while the STN is closely related to neuropsychologically relevant areas and circuits, the GPi does not seem to be so closely related: Vidailhet *et al.* [31] did not see any change of mood and cognition three years after bilateral pallidal DBS for generalized dystonia while slight improvements were noted in concept formation, reasoning, and executive functions. On the other hand, members of the same group had noted a 30% overall decline of cognitive functions 3 months after DBS surgery [12].

Especially three circuits are held responsible for these conspicuities. The first circuit links basal ganglia and dorsolateral prefrontal cortex and leads to dysexecutive syndromes (e.g., deficits in planning, metacognition, self-monitoring or strategic functions). The second circuit connects basal ganglia and the anterior cingulate cortex and accounts for symptoms of apathy (e.g., slowdown of cognitive speed, deficits in initiation, productivity and spontaneity). The third circuit links basal ganglia and orbitofrontal cortex, resulting in symptoms of disinhibition (e.g., distractibility, stimulus-driven behaviour as well as deficits in feedback utilization, decision making and social functions) [for reviews, see 10, 26, 33]. Other common cognitive deficits (e.g., memory, language or visuospatial functions) are usually thought to be secondary to the named difficulties or reflecting cortical Lewy body pathology as well as changes in other transmitter systems [e.g., 5, 17, 33]. An exception lies within procedural learning which is mainly subserved by the basal ganglia and often impaired in PD [14].

Despite good knowledge about the underlying pathology, predictions about the cognitive sequelae of the individual are difficult to make. The population of Parkinson patients is extremely heterogeneous. Many factors have been proved to influence the cognitive profile, including patients' age, age at onset of the disease, duration and severity of PD, premorbid intelligence, level of education, motor symptoms, medication, on- and off-stages or accompanying psychiatric disorders like depression [4, 7, 22, 30]. Also, from a neurosurgical point of view it remains to be determined whether there may be additional or other targets among the above mentioned areas and circuits to optimize benefit of DBS for the patients. Close cooperation between neurosurgeons, neurologists and neuropsychologists will open up new exciting avenues.

Conclusions

The data regarding neuropsychological evaluation of patients who have undergone DBS to various targets need to be further clarified in order to better select the best target for DBS in a variety of disorders, and the patients, their relatives and their doctors need to be informed about the possible sequelae concerning neuropsychological disturbances in order to better decide on an individual basis how to cope with possible problems and to follow the patients with the goal of major sustained improvement of quality of daily living.

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New technology

Acta Neurochir Suppl (2008) 101: 13–21

Printed in Austria

Results by motor cortex stimulation in treatment of focal dystonia, Parkinson's disease and post-ictal spasticity. The experience of the Italian Study Group of the Italian Neurosurgical Society

C. A. Pagni[1], A. Albanese[2], A. Bentivoglio[3], G. Broggi[2], S. Canavero[4], B. Cioni[3], M. D. Rose[5], C. D. Simone[5], A. Franzini[2], A. Lavano[5], A. Landi[6], M. Meglio[3], M. Modugno[7], L. Romanelli[7], L. M. Romito[2], C. Sturiale[8], F. Valzania[8], S. Zeme[4], F. Zenga[9]

[1] Milano, Italy
[2] Neurosurgical and Neurological Departments, Neurological Institute C.Besta, Milano, Italy
[3] Neurosurgical Department, Catholic University, Rome, Italy
[4] Neurosurgical Clinic, University of Torino, Torino, Italy
[5] Neurosurgical Department, University of Catanzaro, Catanzaro, Italy
[6] Neurosurgical Department University of Milano-Bicocca, Italy
[7] Neurosurgical Department, Neuromed, Pozzilli (IS), Italy
[8] Neurosurgical Department, Bellaria Hospital, Bologna, Italy
[9] Neurosurgical Department, St.Anna Hospital, Como, Italy

Summary

Extradural motor cortex stimulation has been employed in cases of Parkinson's disease (PD), fixed dystonia (FD) and spastic hemiparesis (SH) following cerebral stroke. Symptoms of PD are improved by EMCS: results were evaluated on the basis of the UPDRS and statistically analysed. In PD EMCS is less efficacious than bilateral subthalamic nucleus (STN) stimulation, but it may be safely employed in patients not eligible for deep brain stimulation (DBS). The most rewarding effect is the improvement, in severely affected patients, of posture and gait. FD, unresponsive to bilateral pallidal stimulation, has been relieved by EDMS. In SH reduction of spasticiy by EMCS allows improvement of the motor function.

Keywords: Extradural motor cortex stimulation; Parkinson's disease; fixed dystonia; spastic hemiparesis; posture and gait disturbances.

Introduction

Woolsey *et al.* in 1979 [43] reported subthreshold stimulation of the sensory-motor cortex blocked tremor and rigidity in Parkinson's disease (PD). Recently it was observed that subthreshold repetitive transcranial magnetic stimulation of the motor cortex (rTMS) might improve, at least temporarily, akinesia, motor performance and others symptoms in PD [7, 20, 22, 32, 36, 37, 39]. Other movement disorders may be improved by rTMS of the motor cortex: writer's cramp [24, 38]; cortical myoclonus-related epileptic activity; tic symptoms in Tourette's syndrome [8]. Lefaucher *et al.* [19] observed that rTMS of the premotor cortex reduced dystonic motor spasm. Hummel *et al.* [14] observed improvement of motor function in the paretic hand in patients with chronic stroke by rTMS. In cases of central pain (CP) due to basal ganglia and brain stem injury extradural motor cortex stimulation (EMCS), proved efficacious in controlling or reducing hemichoreoathetosis, distal resting and action tremor [15–17, 25, 41, 42] and hand dystonia [12, 13] sometime with improvement of the attending hemiparesis. EMCS improves also intentional idiopathic and post-anoxic Myoclonus [12, 13]. EMCS for PD has been employed, for the first time, at the Neurosurgical Clinic of Torino, directed by the senior author (CAP), in 1999. First results have been reported in various papers and lectures [4, 5, 26–30].

Purpose of this paper is to give an overview of the results obtained by EMCS by the Study Group for Movement Disorders of the Italian Neurosurgical Society in: 1. Parkinson's disease, 2. fixed dystonia, 3. hemiparesis in chronic stroke.

Correspondence: Carlo Alberto Pagni, Via Muratori 30, 20135 Milano, Italy. e-mail: carloalberto.pagni@fastwebnet.it

1. Parkinson's disease

Forty-one patients affected by advanced idiopathic PD, who had got a good response to previous L-dopa treatment, were enrolled in this study. There were 21 male and 20 female, aged 56–81 years; mean age 68.76 ± 6.5 yrs. All the patients had a long history of disease (5–22 yrs, mean 13.95 ± 4.97 yrs). They scored III–V on the Hoehn-Yahr scale. The score of the UPDRS off medication was 49–120, mean 91.173 ± 22.189. The patients were either not eligible for or refused (4 cases) deep brain stimulation (DBS). In some patient L-dopa therapy was no more effective, many of them presenting with long term dopa therapy symptoms (dyskinesia, localized dystonia, motor fluctuations etc.). Before implantation patients were submitted to: neurological evaluation (UPDRS off/on), finger tapping, walking time, PDQL (Parkinson disease quality of life scale) psychiatric and neuropsychological evaluation, brain MRI with gadolinium and functional MRI, neurorehabilitative evaluation, EEG, P300, SPECT (99 mTc-ECD; 123I-DATSCAN; 123I-IBZM). Exclusion criteria were: epileptic seizures, psychiatric symptoms (except drug-induced), severe general internal disease, alcohol or drug abuse, severe cognitive deterioration (only one patient with cognitive deterioration was included). Written informed consent was obtained by the patients and/or their relatives or legal representatives.

A quadripolar electrode (Model 3587A; Medtronic, Inc.) with four contacts in line was introduced in the extradural space, over the hand motor area of one hemisphere, usually opposite to the worst clinical side. Eight cases were implanted bilaterally: only the result of the unilateral stimulation will be reported here. The technique for identification of the motor area (including craniometer landmarks, MRI, functional MRI, neuronavigation, evoked sensory potential, motor cortex stimulation) has been described by Cioni [9]. In the first cases the electrode, before definitive implantation of the stimulator, was connected to an external electro-stimulator for a 7–10 days stimulation test; but in the following cases it was connected directly to the implanted stimulator (Kinetra, ITREL II, Medtronic). Stimulation was performed with current values subthreshold for movement, but with different parameters (Table 1) and several setting of the active electrodes by the various members of the study group.

Identification of the best parameters of stimulation is still matter of debate. Benefits were obtained by many combinations of parameters and electrode setting: good results were usually obtained with 2.5–6 Volt, 150–180 μsec, 25–40 Hz, but also with 3–4 Volt, 90–120 μsec, 60–80 Hz. Stimulation was delivered either all over the day and stopped during the night, or during night and day.

Table 1

	Hz	Pulse width (μsec)	Mono- or bipolar	Volt	Side
1	80	120	bipolar	3–6	unilateral and bilateral
2	40–60	180–210	monopolar cath	3–4	unilateral
3	30	120–180	bipolar	2–2.5	unilateral and bilateral
4	60	60–120	bipolar	3–4.3	unilateral
5	25–50	90–180	bipolar	3–6	unilateral
6	25–45	180	bipolar	2–4.5	unilateral

Table 2

	Follow-up					
Months	3	6	12	18	24	36
Case number	41	33	25	11	10	6

Clinical assessment was performed by UPDRS: a) before implantation: baseline evaluation off-medication and on-medication. b) during treatment: at 1, 3, 6, 12 months and then at least every 6 months: on-medication/on-stimulation and off-medication/on-stimulation. (Baseline evaluation off-medication/off-stimulation has not been repeated during the follow-up; a group of cases is now under scrutiny for that). Movie recordings have been taken before and after stimulation. Patients have been followed-up for 3–36 months (Table 2).

Results

General evaluation

Stimulation induced a significant improvement of the Total UPDRS score ($p < 0.050$ Wilcoxon-test), with respect to the baseline value, in the off-medication condition.

In Table 3 the mean value of the UPDRS off-medication before stimulation and during stimulation at 3–36 months is presented.

What is relevant is that there was no worsening of the Total UPDRS score off medication/on stimulation at long term follow-up (24 and 36 months) in each patient.

Motor function. UPDRS section III

Stimulation induced a significant improvement (up to 23.12%, $p < 0.02$) in the motor score with respect to the baseline value in the off-medication condition (Table 4).

Table 3

	UPDRS total off medication						
	Before	3 mos	6 mos	12 mos	18 mos	24 mos	36 mos
Mean	91.73	70.55	76.76	74.63	74.82	81.04	76.49
Standard deviation	22.89	27.14	24.38	21.45	22.07	22.87	23.26
% difference		−23.09	−16.32	−18.64	−18.43	−11.26	−16.70
Wilcoxon text: $p<0.050$		<0.000	<0.020	<0.020	<0.020	<0.020	<0.036

Table 4

	UPDRS section III off medication						
	Before	3 mos	6 mos	12 mos	18 mos	24 mos	36 mos
Mean	49.66	38.18	45.08	43.32	46.89	44.08	40.17
% difference		−23.12	− 9.24	−12.76	−5.58	−9.78	−19.10
Wilcoxon test: p		<0.000	<0.001	<0.020	<0.054	<0.020	<0.032

Table 5

	UPDRS section III on medication						
	Before	3 mos	6 mos	12 mos	18 mos	24 mos	36 mos
Mean	29.64	23.27	24.62	23.48	26.00	27.90	26.50
% difference		−6.37	−5.02	−6.16	−3.64	−1.74	−3.14
Wilcoxon test: p		=0.041	>0.048	=0.054	>0.054	>0.048	>0.062

Table 6

Range of variation of the UPDRS III off med

	12 mos (%)	24 mos (%)	36 mos (%)
Mean	−12.76	−9.78	−19.10
Min.	+15	-3.4	−8.6
Max.	−38.8	−29	−38.7

Table 7

Variation of axial symptoms. UPDRS items 27+28+29

	12 mos (%)	24 mos (%)	36 mos (%)
Mean	−16.26	−13.35	−15.05
Min	+50	0	0
Max	−80	−50	−40

Stimulation reduced also the on-medication scores but this effect reaches statistical significance (Table 5) only at three months follow-up.

Summing up: a significant reduction in the off-medication UPDRS III score was observed after stimulation, and persisted at long term; improvement was only very moderate in the on-medication state. But it is worth noting (Table 6) that there is a large spectrum of variation between minimal and maximal effect; certain subgroup of patients being well responsive while other not. Reduction of the UPDRS III score reaching a difference of – 38.8% has been observed in some patient and the effect persisted at 36 months follow-up.

Axial symptoms, daily living. UPDRS section III items 27–31

Improvement was observed in activities of daily living, posture, gait, arising from a chair, balance, bradykinesia (and at lesser degree in speech and facial expression) as measured by the UPDRS III, items 27–31 and by the 7 meters walking text. Note (Table 7): for the items 27 + 28 + 29 while the mean reduction is constant up to 36 months ranging −13.35%/−16.26%, at the Wilcoxon Test the variation is significant for the whole series only at 24 months ($p<0.032$).

But in a subgroup of patients, the most severely affected, the maximal reduction is very high, reaching in someone a maximum of −40–80% (Table 7). In those patients, the most severely affected, the improvement of the whole UPDRS III score off medication may be low, but the benefit on those function (UPDRS III 27 + 28 + 29) has a formidable impact not only on the quality of life and patient psychology but also on the assistance needed, so that it is considered by the caregivers to be of relevant significance.

Table 8

UPDRS section IV							
	Before	3 mos	6 mos	12 mos	18 mos	24 mos	36 mos
Mean	8.55	6.27	6.61	5.31		7.4	8.00
% difference		−26.66	−22.69	−37.80		−13.45	−6.45
Wilcoxon test: p		<0.020	<0.020	=0.000		<0.032	

Complication of therapy. UPDRS section IV

Stimulation induced significant reduction of the score (Table 8).

Note: there was a marked attenuation of levodopa-induced dyskinesias and dystonia. The effect on therapy complication persisted throughout the 12 months period but it weakened in the following months owing to the fact that in some cases it was necessary to increase the dosage of levodopa. At 36 months the case number is too small for any statistical evaluation.

LEDD variation

Antiparkinsonian drugs (levodopa and dopaminoagonists) expressed in terms of LEDD, showed a trend to reduction when compared to doses used before surgery, but in the whole series reduction was not statistically significant (Table 9).

While in a subgroup of cases reduction was higher than 30%, in other patients no reduction was possible; a third group of patients was needing an increase in therapy up to 35% (see Ref. [2]).

Quality life

At the Parkinson disease quality life scale improvement was significant up to 24 months evaluation; at 36 months the case number is to small to allow statistical evaluation (Table 10).

Table 9

LEDD variation					
	Before	6 mos	12 mos	24 mos	36 mos
Mean	1068	967.6	828.3	905.7	1031
SD±	423.7	399.2	417.9	376.8	387.2

Table 10

Parkinson disease quality life					
Months of stimulation	6	12	18	24	36
Wilcoxon test	<0.022	<0.022	<0.016	<0.016	no ev.

Summing up: Unilateral EMCS alleviates many cardinal symptoms of PD, i.e., akinesia, tremor and rigidity just as bilateral STN DBS does [18, 34]. Three patients out 41 did not get appreciable improvement while some got a marked improvement up to 50% UPDRS score. But the result of stimulation is unpredictable and the benefit on the various symptoms may be very variable; in some case there is a clear improvement of certain symptoms while others present minor or minimal reduction.

The benefit on limbs tremor and rigidity was bilateral, more evident in the limbs opposite to the stimulated side and was more evident in those patients presenting with lower UPDRS scores. But for instance in severely affected cases (Hohen Yahr grades IV–V), who presented satisfactory improvement of axial symptoms, tremor and rigor did not improve markedly. Improvement of motor dexterity too (UPDRS III – items [23, 26]) was bilateral.

Long term dopa syndrome symptoms, dyskinesia and painful dystonia, have been reduced in most of the patients and up to 90% in some of them (see in [2]). One explanation might be that the doses of dopaminergic drugs were reduced (see ahead), but it is possible that this is an effect of the stimulation itself because it was observed before drug reduction. Clinical fluctuations too may be reduced even if not fully abolished.

There is a subgroup of patients severely handicapped owing to difficulty in standing and deambulation which are significantly improved. Some patient (see Ref. [2]) could not walk, not even with assistance and could neither remain seated or rise from a chair; others presented with severe gait disturbance requiring assistance. During EMCS they could sit more comfortably, get up from the chair, stand and walk, even if for short distance without or with minimal assistance. In one case the stimulator broke due to direct injury; in three it switched off for unknown reason: the clinical picture worsened slowly in some week; the UPDRS score rose up to or higher values than before treatment; stimulation having been resumed, after a few days, benefit recurred.

Statistical comparison between benefits by EMCS and by DBS is impossible mainly because nearly all the patients submitted to EMCS were not eligible for DBS owing to age, general conditions, leucoencephalopathy, white matter ischemic foci, agenesia corporis callosi, cerebral atrophy (four eligible for DBS refused intracerebral procedures). By bilateral subthalamic nucleus stimulation an amelioration of motor symptoms at the UPDRS III, with a mean of 42–67%, has been reported at 6–36 months follow-up (see Ref. [34]) patients being evaluated off-medication/off-stimulation at that very moment. Mean values of amelioration after unilateral EMCS are lower and improvement (in spite that in some case it may persist up to 36 months follow-up) seems to decreases in time (see Tables 1–5). That may be due to loss of efficacy of the stimulation but also to worsening of the clinical picture in such a slowly progressive disease as PD: but in this series the evaluation in off-medication/off-stimulation at 24–36 months is lacking. But at least for certain symptoms, such as tremor and rigor, in certain cases the benefits of EMCS seem to parallel those of DBS, and for posture and gait disturbance EMCS seems to be more efficacious.

The most severe adverse events of DBS, intracerebral haemorrhage and infection, are lacking in EMCS (in one case the stimulating apparatus was removed owing to an extracranial infection). But also cognitive deterioration and changes in mood state, worsening of posture, gait and dysphonia (see Refs. [21, 34]), have not been observed. Two patients presented with transitory allucination but in some case improvement of language and speech has been observed by EMCS (see Ref. [2]). Finally 3 out 42 patients (7%) failed to obtain any improvement: in some series of DBS that value reaches 19% (see Ref. [21]).

The pathophysiological rationale for EMCS in patients with PD is still not demonstrated. In advanced parkinsonism, the primary motor cortex and the lateral premotor cortex are hyperactive [33]. Cortical excitability studies in PD revealed an increased excitability of the corticospinal projections at rest, either concomitant to, or resulting from a reduced intracortical inhibition. In addition, basal ganglia and cortical neurons have shown a tendency to oscillate and synchronise their activity in the so called antikinetic beta band (13–30 Hz), as demonstrated by recording in humans during functional neurosurgery [3]. EMCS may restore the normal intracortical inhibition acting on small inhibitory interneurons within the motor cortex as postulated for its application in CP; or it may desynchronise the pathological oscillation on the beta band, or it may act through both mechanisms. The clinical changes induced by EMCS are usually delayed (1–4 weeks); therefore the time-consuming processes of synaptic plasticity, long-term potentiation or depression, expression of secondary messengers, or polarisation of brain tissue may be hypothesised as mechanisms of action [9, 33]. Finally, EMCS might provide clinical benefit by acting not only on cortical structures, but also on remote subcortical structures that are involved in motor control (see Refs. [9, 11, 33]). Bi-directional interconnectivity between motor cortical areas and other neural structures, located in the cortex, basal ganglia, or thalamus could explain why EMCS may induce bilateral effects even if delivered unilaterally. An experimental basis for EMCS in Parkinson's disease was given by Drouot *et al.* [11]. In a primate model of Parkinson's disease they observed a marked functional recovery following motor cortex stimulation with improvement of motor symptoms and bradikinesia.

It is actually unknown why EMCS over the motor area of the hand may improve axial symptoms; however, it has to be taken into account that axial symptoms are thought to be related to a dysfunction of cortical areas. Moreover, the topography and the extension of the somatotopic representations within the motor cortex showed modifications in PD patients during the course of the disease: the hand motor map is progressively displaced and enlarged [40].

2. Fixed dystonia

Two cases of idiopathic fixed dystonia, i.e. segmental focal immobile postures which never return to the neutral position, have been treated at the Neurological Institute C. Besta by Broggi and Franzini. Patients were two females; the age of onset of the disease was 32 and 37 years. In one patient dystonia involved neck and upper trunk with latero-collis and scoliosis. In the second one there was elevation and anterorotation of the left shoulder, upper limb hyper-adduction and severe kyphoscoliosis: bilateral Globus Pallidum Internum (GPI) stimulation during 18 months had been a failure [35]. Both presented sympathetic like painful dystrophia. Psychogenic etiology was excluded. Patients were submitted to general anaesthesia: dystonia ceased and recurred before the patient regained consciousness.

The stimulating electrode was implanted on the motor strip over the arm area on the side opposite to the maximal muscular pathological activity. Continuous stimulation was employed. Best parameters were 60 Hz,

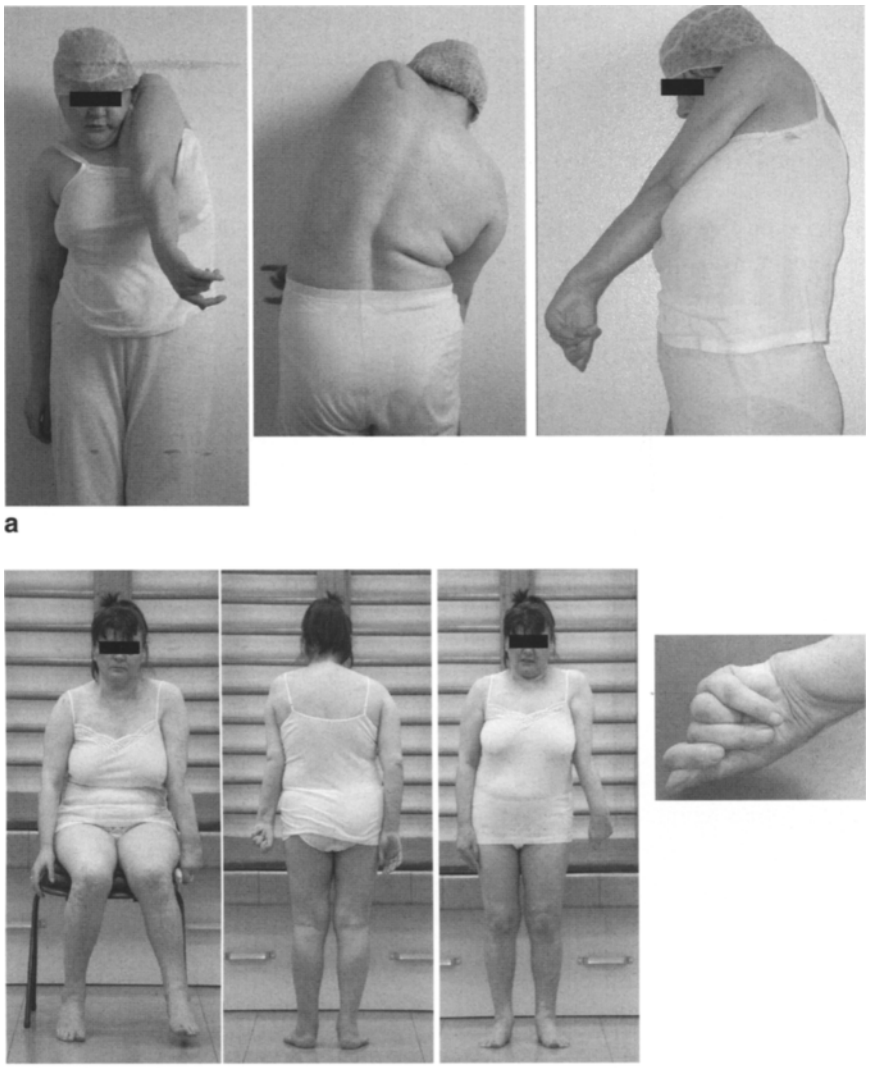

Fig. 1. Fixed dystonia. (a) After 18 months of Globus Pallidum Internum stimulation (b) After 6 months extradural motor cortex stimulation at 60 Hz, 90 msec, 2.8 V. Note that axial and left limb proximal dystonia is fairly well controlled; no benefit on left hand dystonia

90 μsec, 2.8 Volt. Reduction of the dystonic posture began some weeks after stimulation. There was marked improvement in both the cases: axial dystonic posture and limb proximal dystonia was markedly reduced (while there was no improvement of hand dystonia) (Fig. 1). In both the cases the blind test by off-stimulation was followed in a few days by recurrence of symptoms. Other cases are now treated and under scrutiny. Out of them one is worth noting: in a 8 years old boy affected by neonatal dystonia with fixed posture after some weeks of stimulation there was clear improvement of the speech, trunk dystonia being still unaffected. It seems therefore that as in Parkinson's disease unilateral EMCS allows good control of axial symptoms. Moreover EMCS may be effective in cases in which stimulation of the GPI was ineffective.

3. Post-stroke hemiplegia

The members of the Italian Study Group assessed the effect of EMCS on recovery of the motor function in six cases affected by severe or mild hemiparesis, 1–5 years after stroke (five affected also by CP) (Table 11).

The stimulating paddle was implanted on the hand area of the motor cortex of the stroke-damaged hemisphere. (and in one case also on the unaffected hemisphere). Stimulation parameters were: 50–130 Hz, 2.3–7 V, 190–300 μsec with various electrode setting. Continuous stimulation.

Patients were evaluated neurologically and by the European stroke scale (in one case also Fugl-Meyer scale and Bartex Index was included). Results: marked reduction of the spasticity and improvement of the

Table 11

1	66 yrs ♂	L. Thalamic stroke	Left mild spastic hemiparesis. Hand dystonia. Central pain	70% pain relief; reduction of spasticity; hand and harm movement improved
2	45 yrs ♂	L. Fronto-parietal, thalamic and capsular post-hemorrhagic atrophy, and poroencephalia	Right severe hemiplegia (no motor response to MCS). Aphasia. Hand dystonia. Central pain	50% max. pain relief. No effect on hand dystonia and motor function
3	67 yrs ♀	R. Lenticulo-capsular hemorrhage	Left middle spastic hemiparesis. Central pain	Marked pain reduction. Spasticity reduced. Motor performance mild improvement
4	77 yrs ♂	R. Thalamic stroke	Mild paresis and spasticity left upper limb. Central pain	Mild pain improvement. Marked spastiticy reduction and improvement of hand motor performance
5	57 yrs ♀	R. Postoperative lenticulo capsular ischemia	Mild left spastic hemiparesis and pain	Marked relief from pain and motor improvement
6	42 yrs ♂	L. Internal carotid dissection. Large occipito temporal parietal infarct; total destruction of the internal capsule	Right hand monoplegia, severe right arm paresis. Motor aphasia. Right allodynia	Left EMCS no benefit at the hand and wrist level. Improvement of motor performance at the right arm. Right EMCS did not give any benefit

Nos. 1, 2 Franzini [13]. *Nos. 3–5* Sturiale. *No. 6* Canavero [6].

strength and range of motion of the movements was obtained in the four cases affected by lenticulo-thalamic-capsular lesion. All that allowed better physiotherapy. Note that improvement was long lasting and persisted for days after stimulation ceased.

Two cases deserve emphasis (cases no. 2 and no. 6, Table 11). Both the patients were affected by a severe right hand monoplegia, hand and wrist movements being impossible, and by a severe right-arm paresis due to a large cortico-subcortical infarct or hemorrhage destroying the fronto-parieto-temporo-occipital areas and extensively (no. 2) or completely (no. 6) the internal capsule. In one of them motor cortex stimulation did not give rise to motor response (case no. 2 [13]). In the other one, M1-S1 were not activated on fMRI (case no. 6 [6]). In both the cases there was no benefit. In the last one (Case no. 6) even the stimulation of the contralesional healthy side did not improve the motor status. Improvement of hand dystonia and hemiparesis thus seems possible only if motor area and cortico-spinal pathway is not wholly destroyed. It has been reported that motor cortex stimulation by TMS activates brain plasticity favouring post stroke recovery of motor brain mechanism [23]. May be EMCS of the Motor area M1 of the damaged hemisphere, may give rise to neuroplastic changes with better recruitment of the neural circuits within the motor areas and cortico-spinal pathways of the damaged hemisphere and that may contribute to the recovery of motor function (see [1]). An insight on the mechanisms of action may come from clinical neurophysiology. A rTMS study directly demonstrated that motor cortex stimulation can enhance cortico-spinal excitability in stroke [10]. In a right hemiplegic woman the descending cortico-spinal activity evoked by TMS of the lower limb motor cortex has been recorded from the high dorsal epidural space and simultaneously from the tibialis anterior muscle (TA). A standard TMS pulse at 120% of active motor threshold was used for the right motor cortex and a stimulus intensity corresponding to the max stimulator output for the lesioned hemisphere. They compared the evoked spinal and muscle responses before and after iTBS (intermittent transcranial magnetic theta burst stimulation: 10 bursts of 3 pulses at 50 Hz, 80% of active motor threshold were applied at 5 Hz every 10 sec for a total of 600 pulses). After iTBS, the size and number of cortico-spinal volleys evoked by stimulation of the affected hemisphere was increased, and a small MEP previously absent, was recorded from right TA; whereas there was slight reduction of the amplitudes of cortico-spinal volleys evoked after stimulation of the normal side, and reduction of the amplitudes of left TA MEP. After magnetic iTBS, the increase in cortico-spinal activity evoked by stimulation of the lesioned cortex was associated with a decrease in the excitability of the cortico-spinal output in the opposite hemisphere. This suggest a change in the functional connectivity involving both lesional and non lesional hemispheres.

It seems that to get improvement of the motor status in hemiparetic patients neuroplastic changes must develop in the, at least partially preserved, cortical areas (premotor, motor, parietal) and cortico-spinal pathways of the damaged hemisphere. Up to date motor cortex stimulation has been employed, years after the stroke, in cases of stabilized hemiplegia with moderate or minimal improvement (see also [31]). May be earlier application might facilitate neuroplastic changes and better recruitment of the brain areas involved with better motor function recovery.

Conclusion

Unilateral EMCS seems to be a promising tool improving movement disorders. It is less efficacious than bilateral STN DBS in Parkinson's disease but it may be safely employed in patients not eligible for DBS. The most dramatic effect is the improvement, in severely affected patients, of posture and gait. Also Fixed Dystonia of the trunk, unresponsive to deep bilateral pallidal stimulation may be improved by unilateral EMCS. In cases of severe spastic hemiparesis following cerebral stroke EMCS reducing spasticiy may give an improvement of motor status.

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Translational research

Acta Neurochir Suppl (2008) 101: 23–25

Printed in Austria

Electrically and mechanically evoked nociceptive neuronal responses in the rat anterior cingulate cortex

B.-C. Shyu, W.-F. Chen, H.-C. Shih

Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, R.O.C.

Summary

The present study examined nociceptive properties of anterior cingulate cortical (ACC) neurons following application of peripheral noxious electrical and mechanical stimulations to anesthetized rats. Among a total of 108 recorded neurons, 59 units were excited or inhibited by noxious electrical or mechanical stimulation. Of these 59 cells, 38% were located in area 24b, another 38% were located in area 8, and the remaining cells were located in areas 24a and 25. The noxious stimulus-responsive neurons were located predominately in layers V (58%) and III (30%), and the remaining cells were located in layers II and VI. The latency of evoked unit activities was 209.75 ± 26.62 ms and the threshold of the ACC responses was 10 times greater than that in primary somatosensory cortex (S1). Morphine treatment (5 mg/kg, i.v.) increased activity in evoked ACC neurons. This effect was reversed by naloxone (2 mg, i.v.). Nociceptive neurons in the ACC were distributed in area 24 and motor related regions. The locations and properties of evoked responses indicated that ACC neurons may play a role in avoidance behavior in the context of affective aspects of nociceptive information processing.

Keywords: Anterior cingulate cortex; primary somatosensory cortex; noxious stimuli; single unit activity; morphine.

Introduction

In view of the growing emphasis of the functional role of cingulate cortex in human emotional pain experiences, the rat ACC is an important model in which to study the nociceptive mechanism underlying human pain. Because the commonly used rat brain atlas of Paxinos and Watson [7] does not follow the Brodmann nomenclature, results obtained from rodent studies cannot readily be compared to results obtained in studies of the human medial prefrontal cortex. As a result of this incongruity in nomenclature conventions, there is a growing gap between rodent nociception studies and human pain neuroimaging. Brodmann's scheme was modified for adaptation to rat cingulate cortex by Vogt and Peters [10], and that adaptation was subsequently related to human cortex. In a recent review article, Vogt summarized a comparative neuroanatomical study and demonstrated that each cingulate area in rodent can be related to analogous areas in primate cortex [11]. Assessing the relevance of rodent models to nociceptive mechanisms of human pain pathology is essential to define relationships between each cytoarchitectural area in rodent with those in the primate medial prefrontal cortex. Thus the aim of the present study was to evaluate the cortical distribution of nociceptive neurons in the rat ACC according to the Brodmann scheme and nomenclature. Properties of nociceptive unit activities were further evaluated following morphine and naloxone treatment.

Correspondence: Bai-Chuang Shyu, Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan, R.O.C.
e-mail: bmbai@gate.sinica.edu.tw

Materials and methods

Fourteen male Sprague-Dawley rats (body weight 250–350 g) were anesthetized with 4% halothane (in 100% of O_2). After tracheal catheterization, each animal was maintained under anesthesia with 1.0–1.5% halothane and a craniotomy was performed to enable electrophysiological recording. The electrical stimulation consisted of a biphasic electrical current (0.03–10 mA, 0.5 msec duration, 0.1 Hz) delivered to the sciatic nerve by an isolated pulse stimulator (Model 2100, A-M Systems, Carlsborg, WA, USA). Evoked field potentials and unit activities in the ACC and primary somatosensory cortex (S1) were recorded via a glass micropipette filled with 3 M NaCl. The extracellular field potentials were amplified by a high input impedance amplifier (Axoclamp-2A, Axon Instruments Inc., USA). All analog signals were sent to a PC-based data acquisition system for on-line A/D conversion and digital analysis.

Results

Electrically evoked nociceptive responses in the ACC and S1, including a post-stimulus histogram and an av-

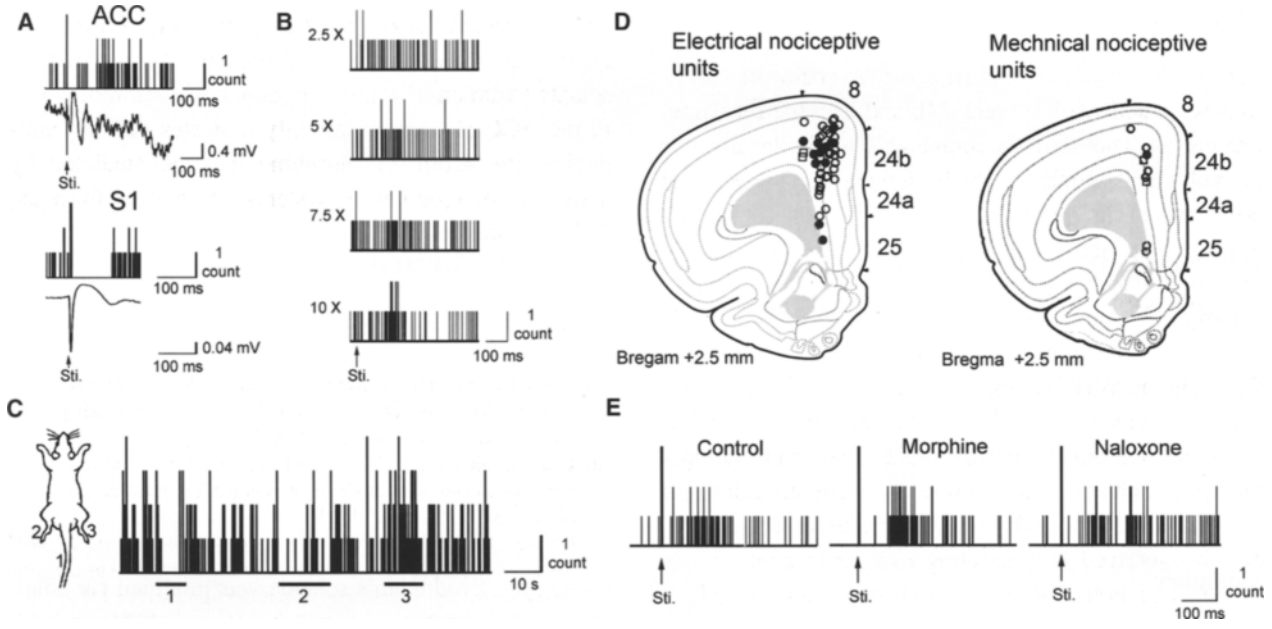

Fig. 1. Properties, cortical distributions and morphine effect of the nociceptive units. (A) Electrically evoked unit activities in the ACC (*upper panel*) and S1 (*lower panel*). Upper sweeps in each panel show a post-stimulus histogram and lower sweeps of each panel are the averaged field potentials. (B) Evoked unit responses in the ACC following a range of graded electrical intensities. (C) Unit activities evoked by noxious mechanical stimuli. The horizontal black bars indicate the time periods during which the following stimuli were applied: *1* tail, *2* left hind paw, and *3* right hind paw. (D) Cortical area and layer distributions of the electrical and mechanical evoked unit responses in the ACC. Open circle: unilateral excitatory response, *solid circle*: bilateral excitatory response, and *open square*: inhibitory response. (E) Morphine (5 mg/kg, i.v.) and naloxone (2 mg, i.v.) effects on evoked ACC nociceptive units

eraged field potential recorded from the same unit, are depicted in Fig. 1A. Both unit and field potential recordings in the ACC indicated a late onset of the evoked responses relative to that in S1. The latency of the evoked unit response in the ACC was 209.75 ± 26.62 msec ($n = 10$) by contralateral stimulation and 221.76 ± 35.02 msec ($n = 10$) by ipsilateral stimulation. Meanwhile the latency for inhibitory responses was 145.00 ± 16.07 msec ($n = 5$). Examples of responses in the ACC by graded electrical stimulus intensity (2.5, 5, 7.5, and 10 times threshold) are shown in Fig. 1B. A marked unit response could be activated by stimulation of an intensity that was 10 times the threshold intensity.

Table 1. *The number and percentage of electrical and mechanical evoked nociceptive units*

Stimulation modes	Effect	Side	Number	%
High intensity electrical	Excitatory	Unilateral	31	62
		Bilateral	13	26
	Inhibitory		6	12
	Total		50	100
Noxious mechanical	Excitatory	Unilateral	6	67
		Bilateral	1	11
	Inhibitory		2	22
	Total		9	100

A typical example of an ACC unit activity response to is shown in Fig. 1C. ACC units had excitatory responses to left hind paw [3] pinch, but inhibitory responses to both tail [1] and right hind paw [2] pinches. The numbers and percentages of the units evoked by noxious electrical or mechanical stimulation are summarized in Table 1.

Of the 108 neurons that were recorded in the ACC in 14 rats, histological examination revealed that 38% ($n = 41$) of the nociceptive neurons were located in the cingulate cortex, in a region designated as area 24b. Another 38% ($n = 41$) were distributed in secondary motor cortex, in a region designated as area 8. Meanwhile the remaining nociceptive neurons were located in areas 24a and 25. 58% and 30% of responsive neurons were located in layers V and III, respectively, while the remaining nociceptive cells were located in layers II and VI. The cortical area and layer distributions of units that exhibited nociceptive responses are illustrated in Fig. 1D.

Intravenous injection of morphine (5 mg/kg) enhanced evoked unit responses in the ACC ($P < 0.01$, $n = 5$) as evidenced by the post-stimulus histograms shown in Fig. 1E. This effect was completely reversed by a naloxone injection (2 mg/kg, i.v.).

Discussion

The present results demonstrated that nociceptive neurons were activated in areas 24b and 8 in the rat cingulate cortex. This result is comparable to similar findings in rabbit and monkey, which showed the presence of nociceptive neurons in areas 24 [8, 4]. At least tenfold of the S1 threshold intensity was required to elicit distinct unit responses in the ACC. We have previously determined that nociceptive A-delta afferent fibers could be excited by stimulation 10 times that of the somatic threshold intensity [2]. Thus it is very likely that the afferents driving the unit activities in the ACC are nociceptive.

Studies demonstrating that nocifensive and inflammatory pain behaviors are significantly altered following lesioning of areas 24b and 8 indicate that the ACC may be involved in generating avoidance behaviors in response to potential or actual tissue injury [3]. It is worth noting that there are substantial reciprocal connections between visual cortex and areas 24b and 8 [9]. Furthermore, area 8 is connected to other motor areas and corticospinal neurons have been found in area 24b. Thus it suggests that these two cortical areas play an important role in visuomotor integration that is critical for prediction and avoidance of painful situations.

The morphine-induced excitation of nociceptive units in the ACC observed in the present study was likely the result of a collective action of morphine on multiple levels of the ascending nociceptive pathway. However, it is worth noting that our previous study showed that morphine can also act locally within the intracortical circuitry [12]. And moderate to high levels of mu-opioid receptors are present in the ACC [6]. Thalamocingulate projection fibers terminate on opioid interneurons and GABAergic interneurons, as well as on principal neurons in the ACC [5]. Thus it is possible that morphine enhancement may be mediated through inhibition of GABAergic interneurons by opioid interneurons in the ACC. A recent human neuroimaging study showed that analgesia induced by μ-opioid receptor agonist was associated with an increase of regional cerebral blood flow in the ACC [1], which strongly indicates that the antinociceptive action of morphine may be mediated by activation of modulatory systems descending from the ACC to subcortical areas.

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Traumatic brain injury

Acta Neurochir Suppl (2008) 101: 27–33

Printed in Austria

Trigeminal neuralgia. Non-invasive techniques versus microvascular decompression. It is really available any further improvement?

C. A. Pagni[1], L. Fariselli[2], S. Zeme[3]

[1] Milano, Italy
[2] Neurosurgical Department Fondazione Istituto Carlo Besta, Milano, Italy
[3] Neurosurgical Clinic, University of Torino, Torino, Italy

Summary

Analysis of the results of the various methods for treatment of typical trigeminal neuralgia (TN) based on the literature and personal experience. The personal experience includes 847 cases: total thyzotomy in the posterior fossa 17 cases; rhyzotomy in the posterior fossa sparing the intermediate fibers 16 cases; microvascular decompression (MVD) 141 cases; controlled thermorhizotomy (PTR) 54 cases; Fogarty Balloon compression (FBC) 223 cases; glycerol ganglyolis (PGG) 12 cases; miscellaneous 48 case; medical treatment only 310 cases; cyberknife radiosurgery (CKR) 46 cases. The follow-up in this series is 1–32 years. MVD of the Vth cranial nerve in posterior fossa gives the best results in term of long-term pain relief without collateral effects in drug-resistant TN. Percutaneous techniques (PTR, PGG, FBC) are indicated in patients either without neurovascular conflict or with excessive surgical risk.

Stereotactic radiosurgery (SRS) and CKR might be considered an improvement of percutaneous and surgical techniques, but contrary to the expectations, the rate of complete pain relief at long term is lower. SRS and CKR are less effective than MVD which, in spite of the risks it entails, remains the choice treatment for typical trigeminal neuralgia.

Keywords: Typical trigeminal neuralgia; microvascular decompression in posterior fossa rhizotomy; percutaneous techniques; stereotactic radiosurgery; cyberknife radiosurgery.

Introduction

Various surgical methods for treatment of typical trigeminal neuralgia (TN) are on the scene since at least 100 years. The goal of treatment should be permanent relief from the attacks without any neurological impairment with minimal incidence of recurrences. Only microvascular decompression (MVD) of the Vth cranial nerve in the posterior fossa seems to get this goal. Other more or less demolitive surgical procedures entail at least a more or less marked facial sensory defect and/or are associated with high percentage of recurrence. Stereotactic radiosurgery (SRS), introduced in the last few years, has been claimed as the best non-invasive technique and proposed as a valid substitute of all other available surgical methods. Purpose of the paper is to put, on the basis of the literature and personal experience, this statement in its true perspective.

Correspondence: Carlo Alberto Pagni, Via Muratori 30, 20135 Milano, Italy. e-mail: carloalberto.pagni@fastwebnet.it

Hystorical review

Both partial or total rhizotomy by subtemporal route (Frazier) or *via* posterior fossa (Dandy) give a very high rate of success with immediate relief from pain attacks (up to 99% in some series) [31, 68]. At long term follow up, in partial rhizotomies, recurrences have been reported in 15–30% of the cases [39, 66, 68]. Total rhizotomy *via* the posterior fossa gave 100% of initial relief and no recurrence (up to 32 years follow up in our series, Table 1). Both the procedures were not devoid of complications and presented a severe burden of sensory deficits: more or less extensive facial numbness in all the cases; annoying dysesthesia up to 27% and painful anaesthesia up to 10% of the cases following partial rhizotomy (incidence being lower following partial section *via* posterior fossa than following Frazier's operation); dysesthesia in 15% and anesthesia dolorosa in 38% of the cases following total rhizotomy *via* posterior fossa [41]. Moreover total posterior rhizotomy presented high rate of keratitis [41]. The attempt to avoid all that by rhizotomy sparing the accessory fibers of the trigeminal root however failed [31]. Siöqvist's operation, bulbar trigeminal tractotomy [56] did not gain popularity

Table 1

Personal series	No.	F	M	Age (mean)	Follow-up (yrs)
Posterior fossa rhizotomy – total	17	10	7	29–75 (55)	6–32
Posterior fossa rhizotomy – SAF	16	12	4	26–73 (52)	6–27
Microvascular decompression	141	87	54	18–76 (56)	1–25
Controlled thermocoagulation	54	32	22	42–89 (64)	2–30
Balloon compression	223	127	96	34–94 (68)	1–27
Glycerol gangliolysis	12	9	3	55–89 (65)	2–25
Miscellaneous	28	17	11	38–80 (61)	2–30
Medical treatment only	310	202	108	23–86 (61)	2–28
Cyberknife radiosurgery	46	26	20	55–78 (64)	1
Total	801	496	305	18–94 (60)	1–32

SAF Sparing accessory fibers.

owing to the operative risks and high incidence of unpleasant dysesthesia, pain and hyperpatia in the hypoalgesic facial territory (up to 65% of the cases; see in Ref. [41]). Less invasive methods of treatment did not give rewarding results. Peripheral neurectomy or alcohol block gave immediate relief in only 85–90% of cases and recurrences numbered more than 50% [68]. Electrocoagulation of the Gasserian ganglion by Kirschner [23] method gave a tremendous amount of facial dysesthesia, painful anesthesia and keratitis. Thus other techniques have been introduced. Decompression according to Taarnhøj [62], compression according to Shelden [55], percutaneous gangliolysis with normal saline [11, 51] and hot saline [18]; phenol in glycerine [20]; mechanical compression by a blunt instrument [21] or myodil and bone wax [14]: all the methods (more than thousand treated patients) allow control of pain attacks in virtually any patient with minimal or nil sensory defect; dysesthesia and painful anesthesia being exceptional. But pain recurrence is observed in more than 40–50% of the cases.

Surgical and percutaneous techniques

More recently other method have been introduced, and are still employed today:

1. Percutaneous controlled thermorhizotomy (PTR) [60] (aiming at selective interruption of the pain fibers from the trigger area)
2. Percutaneous fogarty balloon compression (FBC) [36] (mechanism?)
3. Percutaneous glycerol gangliolysis (PGG) [16] (mechanism?)
4. Microvascular decompression (MVD) [19] (TN being due to nervo-vascular conflict at the root entry zone permanent relief might be obtained by microvascular decompression keeping away the offending vessel from the trigeminal root; see [42])

Our experience included also those techniques (Table 1).

The four procedures are effective treatments for trigeminal neuralgia. Thousand cases have been treated in the last twenty years.

Evaluation of the literature results may be difficult owing to: the heterogeneous nature of the data; lack of uniformity in terms of evaluation of the outcome; evaluation of the success in relation to sensory complications; rate of complete pain relief; definition of pain recurrence; different length of the follow-up. In collecting the data we took into consideration only studies which considered pain totally relieved if patients were pain free without medication, recurrence being any relapse of pain attack (requiring or not requiring further medication or treatment), and with long term follow-up (5–15 years) Rate for success, recurrences, facial numbness, dysesthesia, painful anesthesia, corneal reflex loss and keratitis, trigeminal motor weakness is given in Table 2.

- Percutaneous controlled thermorhizotomy (PTR) van Loweren *et al.* [62] (700), Broggi *et al.* [7] (1000), Taha and Tew [63] (500), Oturai *et al.* [40] (185), Scrivani *et al.* [52], Kanpolat *et al.* [22] (1216), Taha *et al.* [64] (154). Follow-up: up to 15 years. Personal case series [54]; follow-up: 2–30 years (mean: 8.5)
- Percutaneous glycerol ganglyolisis (PGG) Hakanson [17] (100), Saini [50] (556), Waltz *et al.* [67] (200). Personal cases series [12]; follow-up: 2–25 years (mean: 7.3)
- Fogarty balloon compression (FBC) Broggi *et al.* [7] (206), Abdennebi *et al.* [1] (200), Skirving et Dan [57] (496) Follow up: max 20 years, mean 11 years. Personal case series (223): follow-up: 1–27 years (mean: 6.8)

Table 2

	PTR (%)	PGG (%)	FBC (%)	MVD (%)
Initial pain relief	96–99	80–96	93–99	96–98
Recurrence rate	18–27	24–82	31–34	3–24
Facial numbness	95–100	28–60	<72	2–15
Facial dysesthesia	<23	<5	<18	<1
Anesthesia dolorosa	<1.5	<2	<0.5	0
Corneal reflex loss	<8	<4	<2	0
Keratitis	<1	<2	<1	0
Motor complication	<24	<2	<66	0

Data from cases series of more than 100 cases.

- Microvascular decompression (MVD) Klun 1992 (178), Kondo 2001, Sindou et Mertens [54] (120), Taha *et al.* [64], Taha and Tew [63], Barker *et al.* [4] (1185) Broggi *et al.* [9] (250). Personal cases series [141]: follow up: 1–25 years (mean: 6.3)

Significant complications (meningitis, temporal lobe haemorrhage, epileptic seizures, stroke, diplopia, including death) are exceedingly rare with percutaneous procedures totalling 0.2–2% in many thousands of cases [1, 7, 8, 17, 22, 50, 52, 59, 65, 67].

In MVD CSF leakage, meningitis, cerebellar haemathoma/infarct (1 case out of 141 cases in our series), hydrocephalus have not been reported in certain cases series and are reported less and less frequently in the most recent series [3, 9, 38].

The most frequently reported complication of MVD, hearing loss, sometime permanent, occurred in up to 3% of patients before 1990 [7, 15, 54, 61, Personal series] but it can be reduced by careful surgical handling (high supracerebellar approach to the V, avoiding the VII–VIIIth manipulation and neurophysiological control [3, 4, 33, 55].

Of course posterior fossa surgery entails a certain mortality risk. But also percutaneous techniques are not devoided of that [1, 16, 58]. Sweet [59] reported 15 deaths (0.2%) in a collected series of more than 8000 PTR. In the past mortality rate for MVD was about 1%: but in the most recent series, since 1995, the rate is greatly reduced: zero mortality out of 696 cases (Table 3) (3, 9, 35, 38, 43, Personal series). A mortality rate of 0.3% has been observed in recent series [4, 34].

By percutaneous techniques facial numbness has been reported in at least 60–70% of the cases: this is usually not annoying but 20% of patients treated by PTR and FBC complains of dysesthesia and/or anesthesia dolorosa affecting their life quality. (The difficulty in evaluation of facial numbness, dysesthesia and painful anesthesia has been discussed by Pagni [41]). In a paper by Lopez *et al.* (29 bis) comparing PTR, PGG, and FBC the conclusion had been reached that radiofrequency offers the highest rates of complete pain relief. More than three-quarters of the patients treated by PTR and by PGG were pain free at 6 months after treatment. More than 60% of the cases treated by PTR were still pain free at 3 years follow-up versus 55% treated by both PGG and FBC, even if there is further decay in the following years.

MVD eliminates pain attacks in more than 98% of the cases with the lesser rate of recurrence (from 3 to 24% in the reported series) at very long follow up (up to 20 years). Facial numbness is reported in less than 15% of the cases; facial dysesthesia is exceptional (no more than 1%). Facial anaesthesia dolorosa, corneal anesthesia, cheratitis is nil.

Summing up we can affirm with confidence that MVD *via* posterior fossa is generally safe and provides better rates of long term complete pain relief with preservation of facial sensibility than any percutaneous procedure. The risks are slightly higher but surgical morbidity has been significantly reduced by refinement of technical

Table 3

MVD Operative mortality rate

No mortality			Mortality		
Author	Pat. no.	Deaths	Author	Pat. no.	Deaths (%)
Meneses *et al.* [35]	48	0	Mendoza and Illingworth [34]	133	1/0.7
Pamir *et al.* [43]	32	0	Barker *et al.* [4]	1185	2/0.2
Broggi *et al.* [9]	250	0	Ryu *et al.*	132	1/0.8
Ogungbo *et al.* [38]	62	0	Tronnier *et al.*	378	3/0.8
Javadpour *et al.*	83	0			
Ashkan and Marsh [3]	80	0			
Personal series	141	0			
	696	0		1828	7/0.3
			Total	7 deaths out 2524 = 0.27%	

manoeuvres. That holds true also for operative mortality that, although higher (7 out 2524 = 0.27%, Table 3), is to day more comparable to the 0.2% rate reported by Sweet [59] and Gybels and Sweet [15] in a series of more than 8000 patients treated by PTR.

Unfortunately an arterial vascular compression of the root is observed at posterior fossa exploration only in about 80–90% of the cases. In the remaining cases presenting venous conflict or no conflict at all, usually patients are submitted to partial root section (Pollock [44] 11% of the cases; Zakrzewska *et al.* [70], 24%). Results after root section in these recent series compares with ancient series, the reported recurrence rate being 18 to 30% [31]. Persistent pain relief is observed in about 75% of the cases with a mean recurrence rate at 5 years of 28% in the series by Zakrzewska *et al.* [70]. That policy however seems to us illogical. There is no reason to inflict a permanent lesion on the root (with the possible attending sensory complications) when the simple manipulation of the root may abolish pain attacks for years [2, 68]: in the case of recurrence percutaneous techniques might allow pain control for further years.

Treatment by stereotactic radiosurgery

Recently an increasing number of patients choose treatment by stereotactic radiosurgery (SRS) as the least invasive procedure for TN after discussing their informed consent with the surgeon but also on the basis of information obtained from Internet and magazines [44]. Many reports have been published about the results of SRS in TN But many studies report only small number of cases; some time do not contain enough patient and result details; results for typical and atypical neuralgia are often given together; follow-up is short; cases of recurrent trigeminal neuralgias following various surgical procedures are included in the series. A small group of papers give sufficient details (some of them using actuarial methodology) to get information on initial pain relief, recurrences and complications [5, 6, 12, 26, 30, 32, 45, 46, 48, 69].

Experience has shown that the minimal radiosurgical dose to get pain relief is 70 Gy at isocenter delivered to a short tract (4–8 mm) of the sensory root while a maximal irradiation dose of less that 90 Gy must be used to avoid permanent trigeminal nerve necrosis [26, 27, 28]. Thus the employed dose was usually 70–85 Gy.

Different target have been employed to improve the results: Kondziolka *et al.* [26, 27] first suggest placing the isocenter 2–3 mm anterior to the dorsal root entry zone into the pons; others just behind the Gasserian Ganglion [47] or on a far-anterior target, the plexus triangularis [32]. Higher rate of success and lower rate of complication have been claimed for each procedure, but in spite of the numerous studies the optimal radiation dose and target remain to be defined [32].

Pain relief following radiosurgery is not immediate: it occurs within 24 h in one third of the treated patients; within one week in 40%. Three quarters of partial and complete responders respond to treatment within three months and over 90% of responses are seen at six months.

However the data, as far as pain relief is concerned, are sometime reported in a misleading way. In most of the papers pain control is rated as: excellent, complete abolition of pain off medication; good, relief of pain on medication; fear, reduction of pain attacks on or off medication; poor, no relief (Barrow scale [48]). But unfortunately often giving the total outcome excellent results, that is patients free from pain off-drug, are not given separately but are pooled with patients with total or partial relief on-drug. The initial pain relief (total or partial, off or on drugs) is thus considered as excellent in about 70% of the patients [30, 32], only approximately 25–30% of patients failing to get sufficient pain relief. At long term really total control of pain is obtained in fewer than half of the treated patients who are able to stop drug treatment indefinitely. In fact pain free outcome without medication at long term follow-up ranges between 22 and 76% of the cases in various series (see

Table 4

Author	No.	Dose, gray	F-up	P. free	P. rel	Rec.
Kondziolka *et al.* [26]	106	70–80, 94%	18	60	77	10
Young *et al.* [69]	110	70–80, 93%	19.8	76	88	34
Rogers *et al.* [48]	54	70–80, 100%	12	41	71	21
Brisman and Mooij [6]	179	70–80, 100%	15	52	79	NA
Kondziolka *et al.* [29]	220	70–80, 95%	24	40	69	14
Pollock *et al.* [46]	117	78–80, 56%	26	58	85	16
Brisman [5]	293	70–80, 100%	23	22	76	24

RGy Radiation dose in Gray and percentage of treated patients. In the series of Pollock *et al.* another 44% of cases has been treated with more than 80 Gy.
No Number of patients.
F-up Median follow up, months.
P. free Percentage of pain free outcome without medication.
P. rel Percentage of pain relief. *Rec* Percentage of recurrences.

Table 4) while pain relief, that is absence or reduction of pain attacks on medication is of course higher and may be rewarding in some patients who can get a significant improvement in life quality in spite of some persisting attacks. But strictly speaking any case in which complete pain relief (that is freedom from pain without medication) is not attained should be considered a failure: in that case treatment failure rate is superior than reported.

There were no deaths, general complications or, up to date, cases of induced malignancy [13]; hearing loss, facial paresis and loss of taste have been reported [37, 46].

Factors which seem to influence the outcome of SRS treatment are: higher dose radiation [45], a target closer to brain stem [6], low dose irradiation of the brain stem [32], previous surgical treatment [6, 26, 27].

Trigeminal sensory deficit are seen in about 10–25% of the cases with low doses. But incidence of new sensory defects rises to 50% with 85 Gy and up to 67% with more than 90 Gy [44, 45]. No report is given on keratitis. In spite of the fact that in no series submitted to SRS the term "facial painful anesthesia" has been employed there is a rather high incidence of annoying dysesthesia which affect the quality of life: that increases in cases with more marked sensory deficits and submitted to higher dose radiation, reaching more than 10% in patients treated with 90 Gy [44, 45]. And last but not least sensory trigeminal defect correlates with good pain relief. In the past had been reported that increasing of the dose from 70 to 90 Gy did not give improvement on pain outcome. More recent reports are of the opposite view. Pollock [44] stated that at radiation doses below 80 Gy less than 40% of patients are pain free without medication at 3 years follow up; conversely at radiation doses above 85 Gy up to 60% patients are pain free without medication 3 years after treatment. And Massager *et al.* [32] in a series treated by 90 Gy, concluded that "a shorter distance between the target and the brain stem, a higer radiation dose delivered to the brain stem and the development of mild facial numbness are statistically significant factors for effective pain control".

Table 5

Author	Initial failures (%)	Recurrence
Young *et al.* [69]	12	34%
Maesawa *et al.* [30]	15	17%
Pollock *et al.* [45] 70 Gy	15	30%
Pollock *et al.* [45] 90 Gy	7	15%
Pollock *et al.* [46]	14	20%
Rogers *et al.* [48]	11	21%
Flickinger *et al.* [12] 1 isocentre	16	41%
Flickinger *et al.* [12] 2 isocentres	18	??
Massager *et al.* [32]	17	8% ? mean 13.2 mths.

Table 6

Sheehan *et al.* [52a]	Follow up 3 yrs	
Pain free, last follow-up	total	44% 60/136
	typical TN	46% 56/122
	atypical TN	29% 4/14
Some pain, last follow-up	total	56% 76/136
Recurrence	total	24% 33/136

Recurrences are observed mainly in the first year and are more frequent in patients who had been submitted to previous percutaneous or surgical treatments; initial failures may account for 18% of the treated cases (Table 5).

The paper by the late dr. Steiner [52a] reflects all that. A series of 122 cases of typical and 14 of atypical trigeminal neuralgia has been treated; 14 patients were submitted to radiosurgery twice and one patient three times. The median dose was 80 Gy (70 in 43%, 80 in 55%, 90 in 1 patient). Doses less than 70 Gy were given only on repeated treatment. Targeting centre was 2 to 4 mm anterior to the pons: in 52% of patients the trigeminal nerve was covered with the 50% isodose outside the brainstem; in 43% the 50% isodose curve was adjacent to the brain stem. The median interval from treatment to symptom improvement was 24 days (range 1–189 days). The median follow-up was 19 months. Outcome is given in Table 6.

In conclusion: SRS is an ablative procedure. It is the less invasive surgical technique with low rate of side effects. As in other demolitive procedures there is a direct relationship between post-treatment facial numbness (with the attending sensory complications) and pain relief, the effects of radiosurgery being brought on by non-selective axonal injury up to some months after treatment [28], (the irradiation of the brainstem with low dose 10 to 15 Gy playing probably a role [32]).

Introduction of cyberknife radiosurgery (CKR) [49] raised new hopes by potentially improved targeting accuracy, improved treatment planning and delivery of radiation due to absence of the stereotactic frame and non isocentric homogenous conformal irradiation which can produce homogeneous irradiation along an extended length of the nerve. The hope was to improve efficacy and latency to pain control reducing sensory complications by targeting a longer segment of the nerve. CKR results in a shorter latency for pain relief in front of gamma knife SRS but the result on pain relief seems not better than that by SRS [29]. A series of 46 cases of TN has been submitted to CKR, as first choice treat-

ment, at the Department of Neurosurgery, Radiotherapy, Istituto Neurologico C. Besta, Milano. At 1 year follow-up control of the pain attacks (Barrow Scale 1–3) was obtained in 70% of the patients.

Conclusions

SRS and CKR might be considered an improvement of percutaneous techniques, being less invasive and less discomforting for the patient. But we guess randomised controlled trials with validated outcome measures (i.e. complete freedom from pain off medication, proper definition of recurrences, patients satisfaction and life quality, sensory complications, statistical evaluation of results) are necessary before SRS and CKR might be considered proper substitutes of other techniques. Initially, the rates of pain control by SRS and CKR appear to be in line with other ablative techniques, but contrary to the expectations, the rate of complete pain relief at long term is lower than by MVD: radiosurgery is less effective than MVD which, in spite of the risks it entails, gives the best results in term of long-term pain relief without collateral effects in the cases of drug-resistant TN. MVD remains the choice treatment for typical trigeminal neuralgia. Radiosurgery, as others percutaneous techniques, seems to be a good treatment option for patients unwilling or unable to undergo other surgical procedures and a reasonable second option in recurrences after MVD or in cases in which neuro-vascular conflict is lacking.

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Spinal cord injury

Acta Neurochir Suppl (2008) 101: 35–38

Printed in Austria

Gamma knife radiosurgery for medically refractory idiopathic trigeminal neuralgia

J. H. Kang*, Y. S. Yoon*, D. W. Kang, S. S. Chung, J. W. Chang

Department of Neurosurgery, Brain Korea 21 Project for Medical Science & Brain Research Institute, Yonsei University College of Medicine, Seoul, Korea

Summary

Gamma knife radiosurgery (GKS) has been generally considered as a viable therapeutic option for the management of medically refractory idiopathic trigeminal neuralgia (TN). We reviewed our experience with GKS in patients with TN. Between Feb 1996 and May 2006, 77 patients with medical refractory idiopathic TN were treated using GKS. Thirty-six patients who had undergone other previous procedures, previous GKS, or had brain stem lesion, atypical symptoms, were excluded from this study. Pain improvement was achieved in 38 of the patients with TN (pain response rate 92.7%). Twenty-three patients were pain free and 15 had reduced pain. There were no serious complications. We think that GKS is an effective treatment option for patients with medical refractory idiopathic TN.

Keywords: Gamma knife radiosurgery; trigeminal neuralgia; pain; complication.

Introduction

Several potentially successful surgical modalities are available to patients with medically refractory TN. There is no ideal procedure for any 1 patients and the most appropriate treatment should be decided on a case-by-case basis. GKS is an established therapeutic option for patients with TN [1, 2, 4, 13, 15, 17,18]. The remarkable safety of this procedure has established GKS as a useful therapeutic approach in the management of medically refractory idiopathic TN. To make GKS the first choice of treatment after the failure of medical management, it's efficacy and safety have to strictly evaluated and compared to other surgical procedures.

In our current study, we attempted to identify pain relief and treatment morbidity in radiosurgically treating patients with pharmacoresistant idiopathic TN.

Materials and methods

Patient population

Between Feb 1996 and May 2006, 77 patients with medical refractory idiopathic TN were treated using GKS. The indications of GKS for idiopathic TN were based on the following: the patient's age, overall medical condition, the absence of offending vessel compressing the trigeminal root entry zone on three-dimensional time-of-flight MR imaging, the patient's willingness to undergo radiosurgery, and the recurrence after other surgical procedure.

But, only 41 patients (25 females, 16 males) had typical idiopathic TN without previous surgical procedures. The exclusion criteria are listed in Table 1.

The mean age of the 41 patients was 63.8 years (range 31.6–83.0 years). The mean symptom duration was 58.6 months (range 4.3–300.4 months). The mean follow-up duration was 29.4 months (range 3.0–105.6 months).

With regard to the localization of the pain, 22 patients (53.7%) suffered right-sided facial pain and 19 patients (46.3%) experienced left-sided facial pain. The characteristics of pain distribution are shown in Table 2.

Radiosurgical technique

The trigeminal nerve dorsal root entry zone was targeted in all of our cases. The mean maximum dose used in our series was 84.3 Gy (range 70–90 Gy) and 30% isodose line touched the surface of the pons. The 4 mm collimator was solely used in our series (Fig. 1). The number of isocenter was 1.

Clinical assessment

Exact definitions of the outcome parameters are necessary for meaningful interpretation of our results. "Initial pain improvement" indicates a pain response after GKS regardless of the final result (among this group

*These two authors contributed equally to this work.

Correspondence: Jin Woo Chang, M.D., PhD., Department of Neurosurgery, Yonsei University College of Medicine, CPO Box 8044, Seoul, Korea. e-mail: jchang@yuhs.ac

Table 1. *Exclusion criteria*

Reason	No. of patients
None	41
Follow-up not available	9
Previous procedure	18
Previous GKS	1
Brainstem lesion	2
Atypical symptoms	6
Total	77

Table 2. *Characteristics of pain distribution*

Distribution	No. of patients
V1 only	2
V2 only	7
V3 only	12
V1 and V2	3
V2 and V3	14
V1, V2 and V3	3

are patients in whom doses of medication were reduced after GKS). "Pain free" indicates complete relief of pain at the latest follow-up. "Pain reduction" indicates significant improvement of pain by more than 50% at the latest follow-up examination (none or occasional use of medication for pain control). "No change" means no pain relief at the latest follow-up.

Clinical follow-ups were scheduled at 3-month or 6-month intervals. Statistical analyses were performed using SPSS software (SPSS Inc., Chicago, Ill., USA).

Results

Pain relief and complications

Initial pain improvement was achieved in all 40 patients. The mean latent interval to initial pain improvement was 23.6 days (range 1–125 days) after GKS. One patient did not experience initial pain improvement until latest follow-up, 3.8 month after GKS. The maximum dose used on this patient was 82.5 Gy. Among the 40 patients in whom pain improved initially, 2 patients (2/40, 5%) experienced a recurrence of neuralgia. The latency times to pain recurrence was 8.5 months and 10.6 months following GKS. The maximum dose used on these 2 patients was 70 and 80 Gy. Pain improvement was achieved in 38 patients (pain response rate 92.7%) with 23 patients who were pain free and 15 patients who experienced pain reduction (Table 3). There were no serious complications with the exception of mild facial sensory changes in 11 patients and mild facial nerve dysfunction with mild sensory change in 1 patient (Table 4).

Univariate analysis

Various factors that might influence pain relief and complications were subjected to univariate analysis: age, symptom duration, maximum dose, and pain distribution. The maximum dose was statistically correlated with the GKS outcome (Table 5).

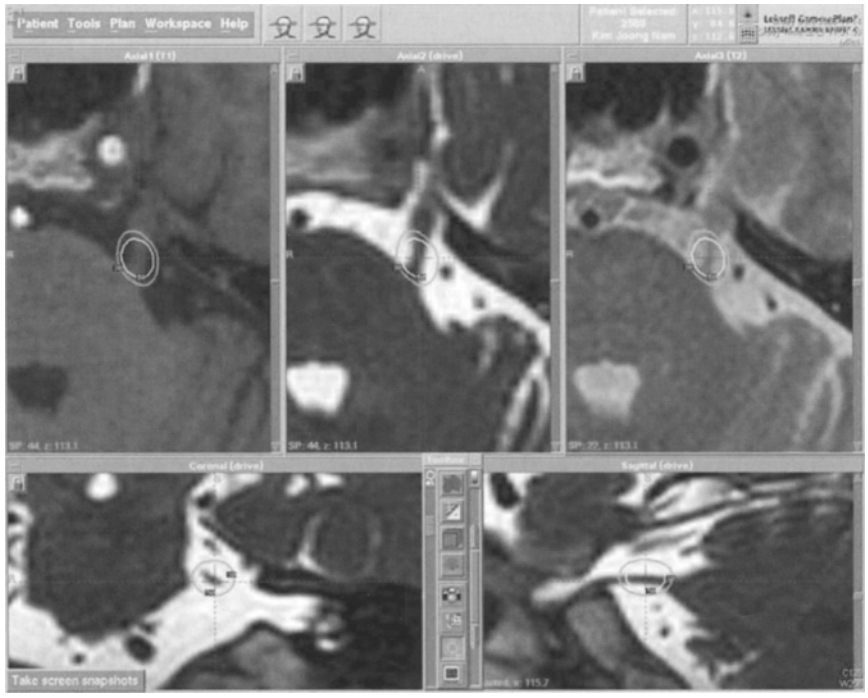

Fig. 1. Characteristic treatment plan in 1 of our patients. A leksell gamma knife gamma plan model B (Elekta Instruments, Atlanta, Ga., USA) was used. 30% isodose line touched the surface of the pons. A 4 mm collimator was solely used in our series

Table 3. *Pain response and maximum dose in patients with TN*

Maximum dose	Free	Reduction	No change	Total
70	0	0	1	1
80	1	1	1	3
82.5	2	2	1	5
85	11	8	0	19
87	3	2	0	5
87.5	5	2	0	7
90	1	0	0	1
Total	23	15	3	41

Table 4. *Complication and maximum dose in patients with TN*

Complication	Maximum dose	No. of patients (%)
Mild sensory change	82.5	1 (20)
	85	6 (31.6)
	87	2 (40)
	87.5	3 (42.9)*

*There was mild facial nerve dysfunction with mild sensory change in 1 patient.

Table 5. *Statistical analysis of various factors related to pain and complications*

Possible factors	Pain relief	Complication
Age	$P=0.576$	$P=0.604$
Symptom duration	$P=0.569$	$P=0.220$
Maximum dose	$P<0.001$	$P=0.091$
Pain distribution	$P=0.072$	$P=0.999$

Probability in univariate and multivariate analyses were based on the cox proportional hazards model.

Discussion

Since Lars Leksell applied his first-generation radiosurgical device to the treatment of TN and reported long-term pain relief in several patients [11, 12], Young *et al.* [20] and Kondziolka *et al.* [5, 7–10] have reported the safety and efficacy of the gamma knife treatment. Now, GKS is considered to be a useful additional therapeutic approach in the management of medically and surgically refractory TN.

The aim of the present study was to analyze GKS effects on patients with no previous surgical intervention. Regarding the initial pain improvement rate, which was 97.6%, this is comparable to the initial pain improvement rates from our published series [2]. Young *et al.* [20] reported an initial pain improvement rate of 95.5% in a large group of patients with typical idiopathic TN who had no previous surgical procedures. In another study [7], they reported an initial pain improvement rate of 96% among patients with no previous surgical procedures, which is slightly lower but still close to our result.

We found that the pain relief rate correlated with the amount of maximum dose received by the trigeminal nerve dorsal root entry zone ($P<0.001$). In our cases we prescribed a maximum dose ranging between 70 and 90 Gy, which is similar to previously published series [5, 13]. The precise dose to achieve excellent results within acceptable rates of complications is still to be defined [3]. Various maximum doses were delivered to different patients within the same study and this made it difficult to compare outcomes of previously published studies and decide the appropriate dose. However, the ideal dose seems to be somewhere between 70 and 90 Gy [16] because pain control was significantly poorer when less than 70 Gy [9] was given to patients, and 100 Gy caused nerve necrosis in baboons [6]. With regard to the pain relief, our outcome analysis shows that patients who received a higher doses were less likely to suffer from pain after GKS.

The most common complication observed in our series was mild facial sensory changes. This complication incidence varies broadly in the literature [9, 13, 14, 16, 20]. In our outcome analysis, no statically significant relationships were identified but there is a suggestion that the maximum dose given to patients may be predictive value within complication ($P=0.091$). Table 4 shows that complication rates increased as the maximum dose given to patients increased. Pollock *et al.* [16] concluded that the incidence of significant trigeminal nerve dysfunction is markedly increased after radiosurgery for patients receiving high-dose radiosurgery. Moreover, 1 patient in our study in whom the maximum dose administered was 87.5 Gy showed mild facial nerve dysfunction with mild sensory change.

In our outcome analysis, there is another suggestion that pain distribution which means trigeminal divisions involved in each patients may be related to GKS outcome ($P=0.072$). Smith and Rogers [19] presented a suggestion similar to ours, that the number of trigeminal divisions involved may be predictive outcome. He reported that patients with pain in a single trigeminal division had a 53% dramatic response rate compared to 41% in patients two divisions involved and 13% of those with all three divisions involved. This suggestion and our analysis results may lead us to deliver higher doses to the patients who present multiple trigeminal division involved.

Conclusions

Our results support the efficacy and safety of GKS for medical refractory idiopathic TN. However, this does

not mean that gamma knife treatment is the best initial treatment for every patient. Further investigation is needed to determine the appropriate dose and determine which patients are likely to benefit from this treatment.

Acknowledgements

This study was supported by a grant (M103KV010031-07K2201-03010) from Brain Research Center of the 21st Century Frontier Research Program funded by the Ministry of Science and Technology in the Republic of Korea and by a CMB-YUHAN research grant of Yonsei University College of Medicine for 2005.

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Stereotactic radiosurgery

Acta Neurochir Suppl (2008) 101: 39–43

Printed in Austria

Stereotactic lesioning for mental illness

M.-C. Kim, T.-K. Lee

Department of Neurosurgery, College of Medicine, Kangnam St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea

Summary

Objective. The authors report stereotactically created lesioning by radiofrequency or Cyberknife radiosurgery for patients with mental illness.

Materials and methods. Since 1993, thirty-eight patients have undergone stereotactic psychosurgery for medically intractable mental illnesses. Two patients had aggressive behavior. Twenty-five patients suffered from Obsessive-Compulsive Disorder (OCD) and ten patients had depression. Another patient suffered from atypical psychosis. Bilateral amygdalotomy and subcaudate tractotomy were done for aggressive behavior. Limbic leucotomy or anterior cingulotomy was done for OCD and subcaudate tractotomy with or without cingulotomy was done for depression. In twenty-three patients, the lesions were made by a radiofrequency (RF) lesion generator. In fifteen cases, the lesions were made with CyberKnife Radiosurgery (CKRS).

Results. The Overt Aggression Scale (OAS) declined from 8 to 2 with clinical improvement during follow up period. With long-term follow up (meaning 57 months) in 25 OCDs, the mean Yale Brown Obsessive Compulsive Score (YBOCS) declined from 34 to 13 ($n = 25$). The Hamilton Depression scale (HAMD) for ten patients with depression declined from 38.5 to 10.5 ($n = 10$). There was no operative mortality and no significant morbidity except one case with transient urinary incontinence.

Conclusion. Authors suggest that stereotactic psychosurgery by RF and CKRS could be a safe and effective means of treating some medically intractable mental illnesses.

Keywords: Stereotactic psychosurgery; obsessive-compulsive disorder; depression; cyberknife radiosurgery.

Introduction

Psychosurgery was defined as "the selective surgical removal or destruction of nerve pathways for the purposes of influencing behavior" in 1976 by the World Health Organization. As "functional" or "limbic system" surgery, neurosurgery has the potential to become a more acceptable treatment for psychiatric diseases [2–4, 24]. With the development of radiation sensitizers and improved delivery vehicles, radiosurgery to treat carefully selected intractable mental illness may become an alternative to prolonged psychiatric therapy.

Correspondence: Tae-Kyu Lee, Department of Neurosurgery, College of Medicine, Kangnam St. Mary's Hospital, The Catholic University, 505 Banpo-dong Seocho-ku, Seoul, Korea 137-701.
e-mail: mckim@catholic.ac.kr

Materials and methods

Demographics

From 1993 to 2006, Thirty-eight patients underwent stereotactic psychosurgery for medically intractable mental illnesses. All the patients were referred by psychiatrists. Two patients had aggressive behavior. Twenty-five patients suffered from OCD and ten patients had depression with anxiety disorders. One patient suffered from atypical psychosis. Bilateral amygdalotomy and subcaudate tractotomy were done for aggressive behavior. Limbic leucotomy or ant cingulotomy was done for OCD and subcaudate tractotomy with or without cingulotomy was done for depression with anxiety.

Target localization

Ventriculography was used in the first seven patients and Magnetic Resonance Image (MRI)-guided stereotaxy was used in recent cases for the localization of target. The lesions were made with a Radionics radiofrequency lesion generator (Burlington, MA, USA) The lesions were always made bilaterally. Our targets for amygdalotomy were 5 mm anterior and 5 mm medial to the anterior tip of the temporal horns or 23–30 mm lateral from the midline. In subcaudate tractotomy target was 12 mm ant from tubercullum sellae, 10 to 15 mm above the floor of the ant fossa, laterally 6 to 14 mm from the midline. We could make a triangular-shaped lesion bilaterally. For Cingulotomy, target was 25 to 35 mm posterior from the anterior part of frontal horn, 5 to 10 mm above the ventricle roof and 10 mm lateral from the midline. Bilateral amygdalotomy and subcaudate tractotomy were done for aggressive behavior. Limbic leucotomy which is combined bilateral cingulotomy with subcaudate tractotomy was done for OCD and subcaudate tractotomy with or without cingulotomy was done for depression with anxiety. In twenty three cases, the lesions were made with radiofrequency lesion generator (Fig. 1) and in fifteen cases (eleven patients with OCD and four patients with depression), the lesions were made with Cyberknife (Sunnyvale, CA, USA) radiosurgery. Computed Tomography (CT) was used in patients for localization of target. A thin-section CT scan (240 slices,

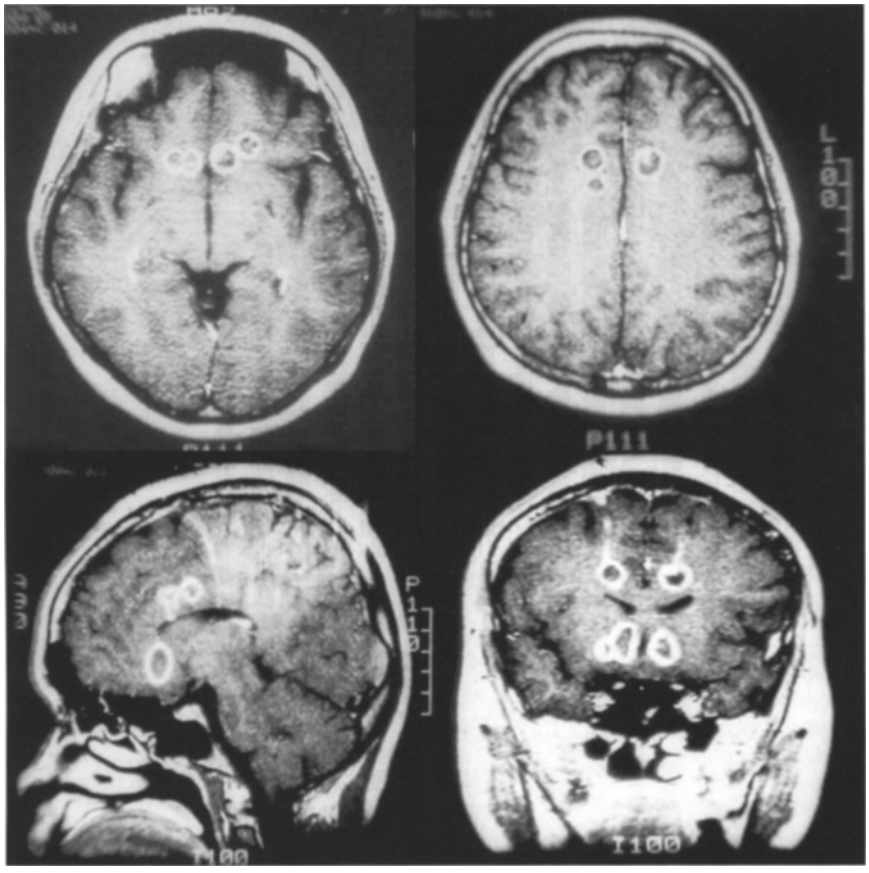

Fig. 1. Postoperation MRI after limbic leucotomy. *Note*: Limbic leucotomy which is combined bilateral cingulotomy with subcaudate tractotomy was done for OCD

thickness 1.0 mm) was made through the entire head, showing the anatomy of ventricle and corpus callosum. The 80% isodose line was prescribed in a conformal fashion to an 7-mm diameter of the target (Fig. 2). We started 75 Gy with 10 mm collimater at 80% isodose line but the necrotic lesion volume was larger than our expectations and now our dose parameter is reduced to 50 Gy with 7 mm collimater at 80% margin dose line.

Treatment protocol

The structured clinical interview for DSM-III-R-Patient Version (SCID-P) was administered to assess current and previous psychiatric diagnoses. A detailed history of the pre- and postoperative course of illness and the current level of psychosocial functioning were recorded. The results of OCD were evaluated with YBOCS, VAS (Visual Analogue Scale) and CGI (Clinical Global Impairment). The OAS, MMS (Mini Mental State) and WAIS (Wechsler adult intelligence scale) were checked for the evaluation of aggressive behavior. Hamilton Depression scale (HAMD) was used for the evaluation of depression.

Results

In OAS scores of aggressive behavior during follow up, scores declined from 8 to 2 with clinical improvement (Table 1). With a long-term follow up (mean 57 months) in 25 OCDs, mean YBOCS decline from 34 to 13 ($n = 25$). Eighteen returned to previous social life. In ten patients with depression with anxiety HAMD declined from 38.5 to 10.5 ($n = 10$). There was no operative mortality and no significant morbidity except one case of mild transient urinary incontinence. In four patients with depression who underwent CKRS, the median score in HAMD declined from 34 to 12 and three patients returned to previous social life. The signal changes in target area were seen in T2-weighted images in MRI performed at 3 months after the treatment. The significant lesions were made with the volume of 0.94 cm^3 and the surrounding margin of low attenuation at 6 months (Fig. 3). With follow up in eleven patients with OCDs after CKRS, the median score in YBOCS of six patients declined from 37 to 23 after 10 months and clinical improvement was observed. T2-weighted images in MRI showed the signal changes in target areas at 6 months after the treatment. There was no operative mortality after CKRS and no significant morbidity except one patient with fatigue and malaise. The RF limbic leucotomy for the 14 patients with OCD improved symptoms in 12 patients (84%) and CKRS induced relief of symptoms in 6 of the 11 patients (54%) with OCD. In ten patients with depression, Six patients had complete relief after RF subcaudate tractotomy and three out of four patients had symptom relief after CKRS.

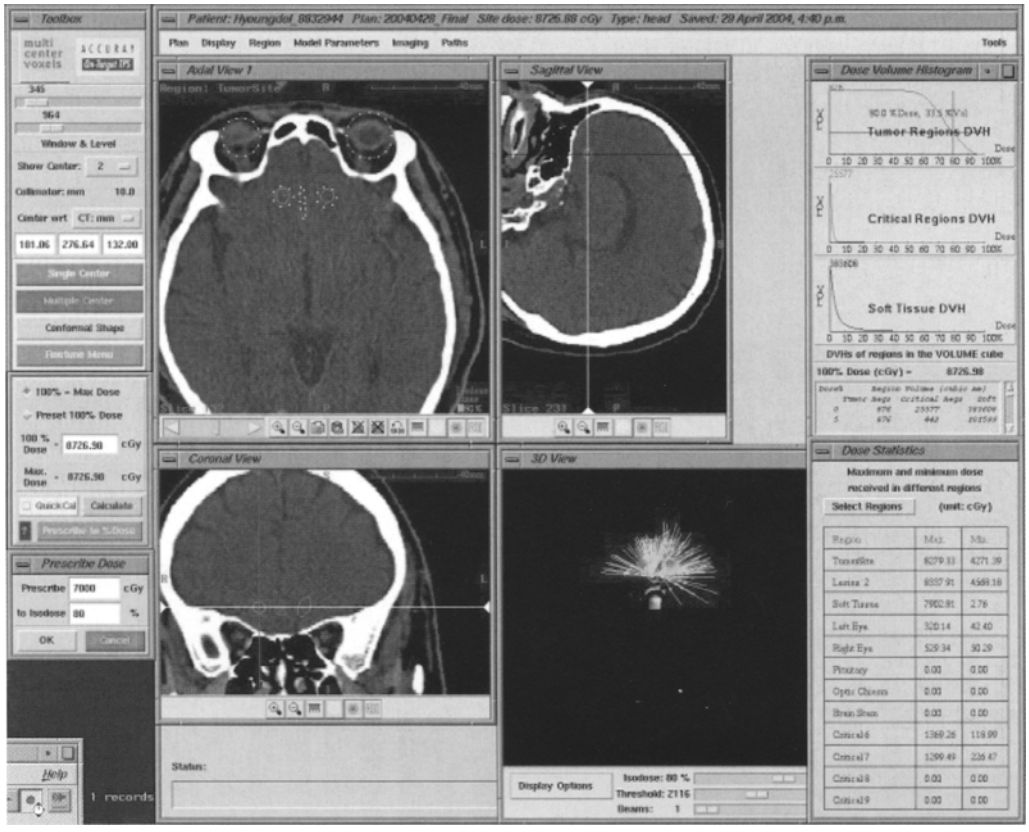

Fig. 2. Bilateral subcaudate tractotomy target in patient with depression. *Note*: In the first patient with cyberknife planning, the subcaudate tractotomy target was 12 mm ant from the tubercullum sellae, 10 to 15 mm above the floor of the ant fossa, laterally 6 to14 mm from the midline. With two sessions, the lesions were made with Cyberknife radiosurgery (Lt: 7000 cGy Rt: 7000 cGy). The 80% isodose line was prescribed in a conformal fashion with an 7-mm diameter of the target

Table 1. *Neuropsychological testing in aggressive behaviour*

	preop	postop 8 yrs
MMS	impossible	17/30
WAIS	impossible	70
CGI	disabled	partially disabled
OAS	12/16	2/16

Note: In aggressive subjects, aggressive behavior fell markedly before 2 months before postoperation. OAS scores during follow up declined from 8 to 2 with clinical improvement.

Discussion

The modern indication in stereotactic neurosurgery for mental illness are refractory aggressive behavior, major depression and OCD [9–11, 14, 16]. The selection of lesion sites in psychiatric disorders was greatly influenced by the proposal of an anatomic basis of emotions in 1937 by Papez [25]. Limbic leucotomy combined bilateral cingulotomy with subcaudate tractotomy, which was introduced by Kelly *et al.* [12, 27]. The dual-lesion technique would produce better functional results than either method alone [18, 21–23]. The use of radiosurgery as a lesion generator for functional neurosurgery already has a 49-year history [17]. Radiosurgery for functional disorders is controversial because physiologic information is not obtained. Experiments in the 1960s showed that high radiosurgical doses (above 150 Gy) delivered to small volumes (3–3.5 mm diameter) caused focal tissue necrosis within one month [1, 13, 15]. With the 4 mm collimator of the Gamma Knife with a dose of 120–200 Gy, radiosurgery lesions in humans were created and the response became unpredictable [13]. In this prospective study of the neuroradiological aspects of Gamma Knife capsulotomy in 11 psychiatric patients, a single-session necrotizing dose of r-irradiation was given to the anterior limb of the internal capsule with the aim of severing frontothalamic fibers by creating a predetermined lesion volume, the size of which was estimated from previous experience [5–8]. The human cerebral reaction to fractionated irradiation has been described by many investigators [15, 17, 19, 20]. Radiosurgery-based psychosurgery has been performed for several decades [17, 26, 28, 29]. To date, only

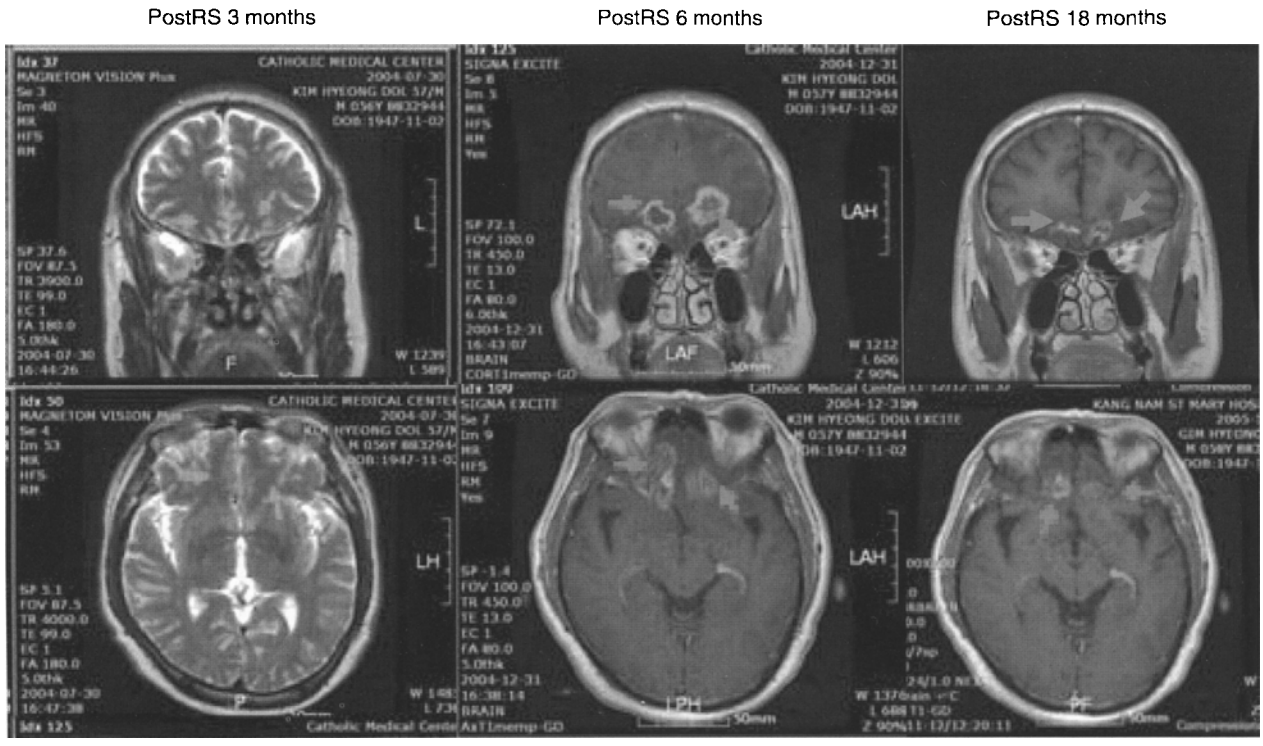

Fig. 3. Postoperation MRI in bilateral subcaudate tractomy. *Note*: MRI shows bilateral radionecrotic change in subcaudate tract area after CKRS

limited data exist that detail the results of radiosurgery for psychiatric disease. We started 75 Gy with 10 mm collimater at 80% isodose line but the necrotic lesion mean volume was 0.94 cm^3 and diameter was 18 mm, and then gradually reduced dose parameter as 50 Gy with 7 mm collimater at 80% margin dose line which we could observe signal change on post treatment MRI. Edema, gliosis, demyelination, and ischemia can all contribute to this signal pattern. The changes of edema and mass effect were also reflected in a decrease of the Huckman numbers in the first postoperative year and, subsequently, an increase after the second postoperative year. Because the mass effect had disappeared at approximately 2 years after the treatment, the high signal is more likely representing demyelination, gliosis, and axon degeneration resulting from the fiber severance [30].

Conclusion

With these long-term results authors suggest that stereotactic lesioning by means of conventional RF and CKRS could be a safe and effective means of treating some medically intractable mental illnesses. Compared with the stereotactic RF lesioning procedure, CKRS disclosed delayed clinical improvement because of delayed ionizing effect and staged radiosurgical procedure. Modern functional neurosurgical procedures treat mental illness and applicate for a subset of psychiatric patients refractory to all other therapies.

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Acta Neurochir Suppl (2008) 101: 47–53

Printed in Austria

Restoration of locomotion in posttraumatic paraplegics: the multidisciplinary approach and unexpected plasticity of single neurons – facts and fantasy

K. R. H. von Wild[1], G. Brunelli[2]

[1] Medical Faculty of the Westphälische Wilhelms-University Münster, Münster, Germany
[2] Foundation for Research on Spinal Cord Lesions, Brescia, Italy

Summary

In Europe there are about 300,000 paraplegics and in every country approximately 1000 new cases per year. Treatment requires a multidisciplinary approach with scientific cooperation targeted to exchange personal knowledge and expertise. At present a completely disrupted spinal cord cannot heal for recovery of motor and/or sensory functioning, although some promising treatment modalities in laboratory animal experiments have been reported. No interventional stem cell procedure so far has shown evidence to restore impaired functioning in human paraplegics. However, functional electrical stimulation (FES) via an implanted neuroprosthesis (SUAW concept) and central nervous system-peripheral nervous system (CNS-PNS) connection have successfully been used for alternative compensatory strategies for voluntary locomotion. This report is to analyse the authors' experience from two European projects in paraplegic. Factors will be identified that might have caused the one or other pitfall since so far both surgical reconstructive procedures have not been adopted by rehabilitation physicians and/or restorative (neuro-)surgeons despite the promising functional results we have achieved. Unexpected plasticity of single neurons following CNS-PNS by-pass procedures is discussed. Future interventions, for example the present phase 1 prospective multiple centre study on the side effects, effectiveness, and reliability of intrathecal treatment of anti-Nogo-A antibodies, are presented and the Chinese stem cell implantation is critically reviewed.

Keywords: Posttraumatic paraplegia; reconstructive surgery in complete SCI; restoration of locomotion in paraplegia; functional electrical stimulation (FES) in SCI; current concepts to improve complete SCI; network of functional neurorehabilitation.

Introduction

Experimental and clinical research in neurotraumatology demands a faithful multidisciplinary approach. This is especially true for the scientific cooperation targeted to exchange the scientist's knowledge within a very important but sensible field of restoration of voluntary locomotion in posttraumatic paraplegics [3, 7, 9–12]. This report is to analyse the authors' personal experience from two European projects to identify factors that might have caused the one or other pitfall since both surgical concepts have not yet been accepted in routine clinical or even experimental re-engineering despite evidentiary clinical results that were later on explained by a series of sophisticated analyses (electroneurophysiologically and gene-bio-technologically) [13, 14]. Unexpected motor cortical brain plasticity [9, 10, 12] by single neurons in the human being with reference to the proven fact that supraspinal neurons can target skeletal muscles retaining the plasticity of generated functional glutamatergic neuromuscular junction in rats following surgical connection of the corticospinal tract with peripheral nerves of the hip mussels is a matter of intensive scientific debate and a mystery to SCI experts. In this context, also future interventions will be mentioned, for example the ongoing phase 1 prospective multiple centre study on the side effects, effectiveness, and reliability of intrathecal treatment of anti-Nogo-A antibodies, just as the Chinese stem cell implantation which is critically reviewed [7, 8, 15].

Methods

Review of the authors' approach by participating in two international experimental clinical projects to establish an international scientific

Correspondence: Dr. med. habil. K. R. H. von Wild, Medical Faculty, Westphälische. Wilhelms-University, Münster, NRW, Frauenburgstrasse 32, D 48155 Münster, Germany.
e-mail: kvw@neurosci.de

network for functional rehabilitation of paraplegics and restoration of voluntary locomotion following complete SCI.

1. Biomed 2 (1997) became known as the SUAW (stand up and walk) project, a European Community scientific research project that followed the first CALIES grant (Computer Aided Locomotion by Implanted Electrical Stimulation in paralysed persons). Directors were Prof. J. Edwards and the late Prof. K. R. Krishnan, University of Salford, Manchester; project management co-ordinator P. Rabischong, Montpellier/France (Fig. 1), with participation of industrials and researchers from Finland, Italy, The Netherlands, Ireland, Great Britain, and Germany. Along with the European CALIES association 9 of 14 technicians were from France. Bernard Denis (Neuromedics) was responsible for industrial partners, assisted by Pierre Couderc (Neuromedics implant). Others were from IBM France and Thomson CSF, Paris, Het Roessingh, R. & DFD, Enschede/Netherlands, and the Fraunhofer Institut St Ingbert/Germany. The surgical procedure consisted of implantation of neuroprosthesis connected with epimyseal and perineural electrodes for FES of the selected hip muscles for locomotion (Fig. 2a–d).

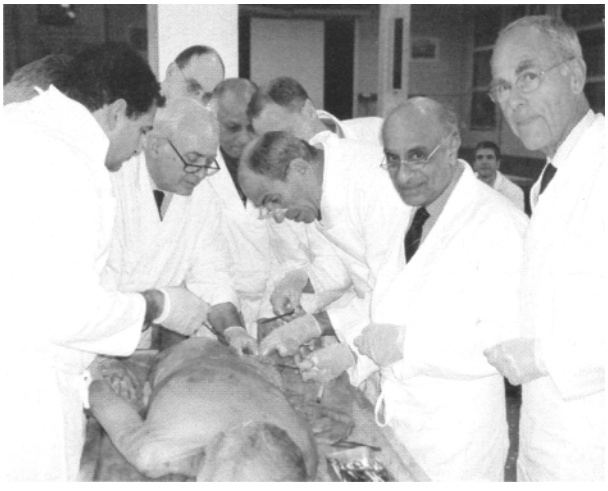

Fig. 1. SUAW cadaver workshop Clermont Ferrand, France, March 26–27 1999. From *left to right*: M. Benichou, P. Rabischong, B. Soni, G. Brunelli, the late K. Krishnan, and KvW

2. CNS – PNS Connection (Brunelli's Paragdigm) (Fig. 3): In prone position connection of the intact ventrolateral corticospinal tract (first motor neuron) above the complete cord lesion via three fascicles of autologous sural nerve grafts on both sides to the receiving stumps of peripheral muscle nerves as they were (from dorsal) the gluteus maximus (hip extension), gluteus medius (abduction and stabilisation of the pelvis), and – after the patient is turned on his back (ventral incision) – the quadriceps muscle (for hip flexion while standing and knee extension).

3. Learning by doing: SUAW matched perfectly the authors' interest in functional neurorehabilitation and re-engineering of spinal cord lesions. Following the project from 1997 to 2002 the authors met during the SUAW cadaver (Fig. 1) and technical workshops when Giorgio Brunelli (GB) raised interest in his CNS-PNS (central nervous system-peripheral

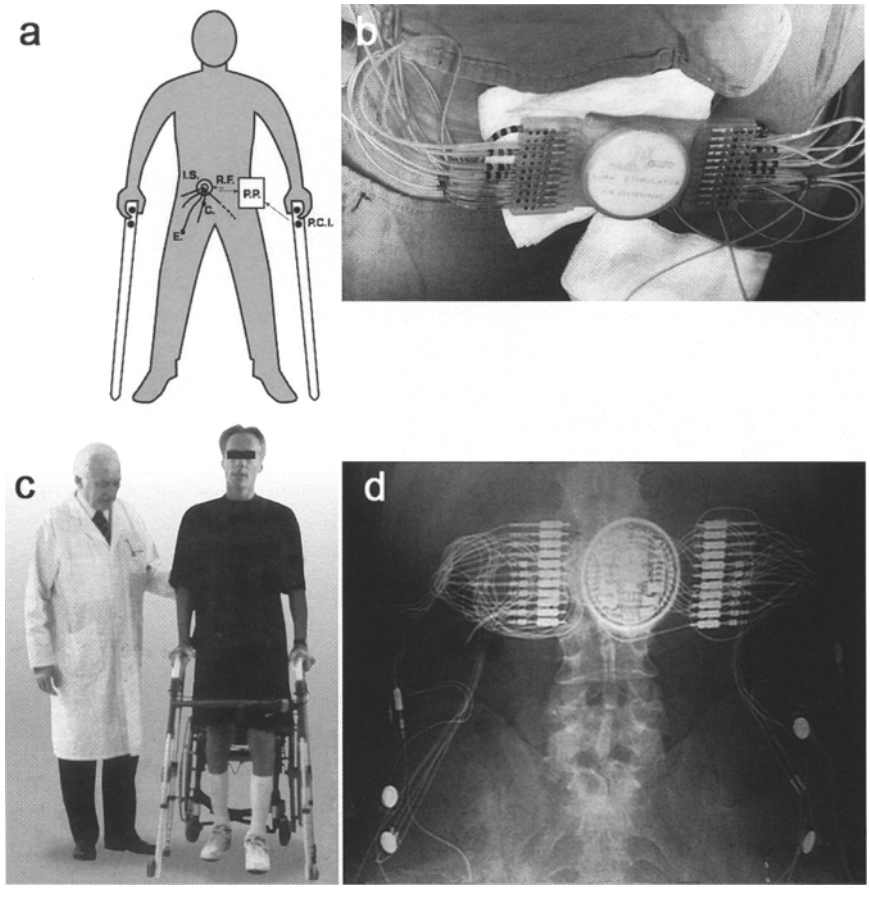

Fig. 2. SUAW concept of implanted FES; (a) Sketch, (c) M.M. two weeks after implantation. (b) FES-neuroprosthesis with cables before and (d) after implantation (X-ray)

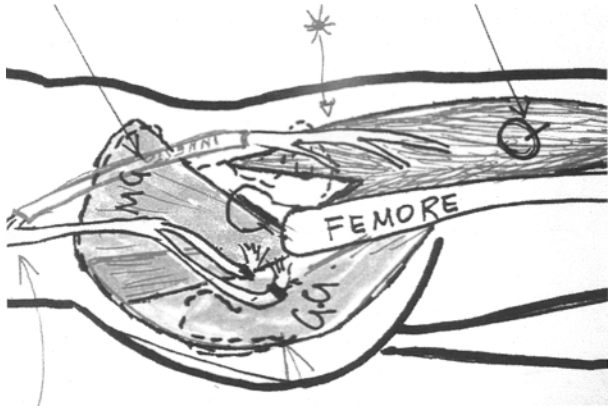

Fig. 3. Sketch of CNS-PNS connection .The ventrolateral bundle T5/6 above the cord lesion (*left*) is connected with the aid of three grafts from the n. suralis on both sides to the maximal and medial glutei muscles and the quadricepos femoris muscle (Sketch by *GB*)

nervous system) paradigm that was ready for use in human beings [1, 2, 4–6].

4. Building up an international neurotrauma network (Fig. 5)

1. Euroacademia **M**ultidisciplinaria **N**eurotraumatologica, (**EMN**) was established in 1995, followed by the **AMN** (World Academy of multidisciplinary neurotraumatology) in May 2002, when GB was a founding member too. The purpose of EMN and AMN is the advancement of neurotraumatology in research, practical application and teaching (see www.emn.cc and www.world-amn.org). Both Academies opened up a friendly direct access to the international members from all fields of neurotraumatology, thus allowing a direct and trustful cooperation and exchange of knowledge. By adhering to this concept, GB jointly organized the 1st AMN congress with his 5th International Symposium on experimental spinal cord repair and regeneration in Brescia/Italy, March 27–29, 2004, in conjunction with the 3rd conference of the WFNS committee of neurorehabilitation, where both surgical concepts were intensively discussed and further studies recommended.

2. Neurological/neurosurgical societies: In 1997, Klaus von Wild (KvW) established the WFNS Committee for Neurorehabilitation that gave way for Prof. Yoishi Katayama, Tokyo, his successor, to establish the International Society of Restorative Neurosurgery (**ISRN**) in 2004. In addition KvW chaired the **EFNS** Panel Neurotraumatology (European Federation of Neurological Societies) in the years 1997 until 2006 and served as a member of **IBIA** Board of Governors (International Brain injury Association). These activities could be combined with the commitment of KvW in the **WFNR** (World Federation for Neurorehabilitation) as founding and Executive Board member since June 2001.

3. Institutions of excellence were selected for performing an international prospective phase 1 study on CNS-PNS paradigm, for which a protocol was set up in 2004: Visiting Consultant at **SAHRA** Rehabilitation Networks University Brasilia, Brazil, 2001, at the INI, Hannover in 2002, at **EL AGOUZA** Armed Force and Rheumatic Rehabilitation Military Hospital and SCI Centre, affiliated with the AIN SHAMS University Cairo, Egypt, 2006, and last but not least at the **CRRC** (China Rehabilitation Research Centre) Beijing, PRCh. Whilst GB is the founder and has been Director of the Foundation for Research on Spinal Cord Lesions, Brescia/Italy for many years, in 2005 he established **ESCRI** (European Spinal Cord Research Institute), Brescia, to promote all studies in the field of SC Lesions, and KvW joined him in his work in 2005.

Fig. 4. Demonstration of voluntary movements following CNS-PNS connection. (a) 1st Gigliola, female, 29 yrs, 16 months after CNS-PNS connection active stretching of both lower limbs via quadriceps femoris muscles and (b) two years after CNS-PNS surgery Gigliola can voluntarily stand up and walk and is even able to climb some steps with support of two sticks that help her keeping her balance despite permanent complete sensory loss T7

Fig. 5. Physical map of the world-marked places indicate the network that was built up by KvW for advertising CNS-PNS connection between 1999 and 2006

Results

Both surgical concepts were performed in parallel after permission of the local regional/national ethical committees in France and Italy:

1. **SUAW:** 28.09.1999 First implantation of neuroprosthesis, Marc M, 38 years, paraplegia T7/8 since 9 yrs due to a car accident (turnover) Surgical team: GB, Dr. M. Benichou (MB), KvW; engineers were P. Couderc, D. Guitaud, K. Koch. Second look Op was necessary to exchange the neuroimplant because of cross talk during first electrical stimulation between epimyseal and perineural electrodes. Second Op at 14.02.2000 was performed by MB and KvW. Postoperative course and FES follow-up have been uneventful up to now (Fig. 2a–d).

Second patient Ludovico, 32 yrs, paraplegia Th 7, 10 yrs after motor scooter accident, was implanted in Imola, Italy, on July 26, 2000, by GB, KvW and MB (same team like in the first Op), assisted now by Dr. Luisa Monini. A second look Op became necessary because one femoral electrode slipped. This procedure was performed by another team in Pisa, Italy, without informing the authors. Replacement of the electrode via an endoscopical approach that was complicated postoperatively by deep infection requiring the total removal of the SUAW implant. The authors were not informed and the last SUAW meeting in Nantes happened without them in March 2001.

2. **1st CNS-PNS connection** (BRUNELLI's Paradigm) on July 20, 2000; Gigliola C, 27 yrs who suffered from complete paraplegia T7 after car accident, just married, so that she strongly demanded surgery from GB for her completely damaged spinal cord. She became the ever first human being who received CNS-PNS connection in analogy to the experiments in monkeys (Fig. 3) with direct neurotisation of her hip muscles. The operation was performed in Imola by the head surgeon GB, assisted by KvW and by Dres. Luisa Monini and Giovanni R. Brunelli.

Second patient Massimo F, 23 yrs, male, followed in June 2003 due to complete lesion T7 after car accident in 2001. The 3rd patient, Vincenzo C, 26 yrs, male, was operated by the same team in January 2004 because of paraplegia T7 after motorbike accident in 1996.

Gigliola started her functional voluntary re-innervation of hip muscles right in time with extension of the lower limbs (Fig. 4a, b) and abduction, flexion, and extension of the re-innervated hip muscles. The video shows her with her first active voluntary locomotion movements in the swimming pool. At present she is able to stand up and to walk voluntarily with the help of two walking sticks up to 80 m either way, of course still limited by paraplegic motor fatigue. She can even climb some steps several times per day and feels happy, although she was divorced within the first year after the operation.

In the two gentlemen functional restoration of locomotion could not be achieved. The main cause might have been the atrophic spinal cord and ventrolateral cortical bundle after too many years following the accidents.

Discussion

Facts: plasticity

Repair of the injured spinal cord means a joint approach of basic and clinical research where restoration of locomotion in paraplegics becomes a challenge for neurosurgeons. KvW took actively part in both projects and reported about the new physiological findings and unexpected functional results. However, neuroscientists, rehabilitation physicians, and the public could hardly or even simply not believe the miracle of restored voluntary locomotion (Figs. 2 and 4) that have become a matter of ongoing debate especially during presentation at international congresses and institutions of excellence (Fig. 5).

Experimental confirmation was meanwhile achieved and was published as the Brunelli Paradigm of CNS-PNS connection. GB and coworkers [3, 11] demonstrated that following the CNS-PNS connection in rat the receptors of the motor end-plates shifted from cholinergic to glutamatergic respectively neuromuscular junction (NMJ) switches from cholinergic type synapse – actylcholine is the main neurotransmitter at the mammalian NMJ – to glutamatergic synapse. This means, the restored neuromuscular activity is resistant to common curare blockers but sensitive to glutamate receptor antagonist in the rat experiments [11]. With regard to restored functioning in human beings, unexpectedly, the reinnervated peripheral hip muscle groups became able to contract individually without co-contractions of the other two muscle groups, notwithstanding the fact that they were connected with axons coming from the same cortical areas. Brain plasticity allows neurons that are placed in different areas and were connected to one muscle fire together, even if remote from each other, for a selected movement. This phenomenon of "brain plasticity by single neurons" is different from the well known "normal" brain plasticity that we call "brain plasticity by cortical areas" [9, 12]. Stunningly, when one muscle contracts due to voluntary command the other muscles do not co-contract with it so that the patient became able over the years to walk with quadripod sticks. We presume that these scattered neurons, connected with a new target, learn and memorize their new capacity while forgetting their previous function, and that also the neurons of the premotor and associative areas must learn the new function and forget the previous one. As early as twelve months after surgery some voluntary activation of the reinnervated muscles appeared and progressed in the following months. Restoration of voluntary functioning of the re-innervated muscles required two years to occur and three years to consolidate. How the brain was able to command one single movement without co-contraction of the other muscles connected with the same corticospinal tract remains an open scientific question to be explained by further functional studies. Plasticity of the brain cortex has been known for many years since fMRI studies have shown changes in the precentral motor area following amputations and transfers of neuromuscular units or of nerves in case of palsies. Intensive physical training has been shown to influence strongly the cortical regions of interest [9, 10, 12].

However, in these cases plasticity concerned the switch of function of one cortical area to a different function: that of the area corresponding to the palsied muscles to compensate its loss of function. In our cases (both experimental and human), on the contrary, not the change of function of an area in its entirety was at stake but a multitude of single neurons scattered in various areas of the cortex changed their target and function firing together for a new selected movement, whereas the other neurons scattered in the same areas but connected with different muscles did not fire. This functional plasticity has not yet been demonstrated nor even presumed before.

New generations of approach have manifested through rodent and non-human primate studies revealing morphologic and physiologic adaptations induced by injury, by learning-associated practice, by the effects of pharmacologic neuromodulators, by the behavioural and molecular bases for enhancing activity-dependent synaptic plasticity, and by cell replacement, gene therapy, and regenerative biologic strategies [9]. The myelin protein Nogo-A is a potent inhibitor of neurite outgrowth in the central nervous system, thus contributing to the incapacity of fiber tracts in the adult spinal cord to regenerate after injury [7, 15]. A joint approach of different research groups is reported to develop a therapy applying anti-Nogo-A antibodies to the injured spinal cord. Clinical groups and rehabilitation engineers have sought to translate this novel strategy into clinical setting. At present, a Phase 1 prospective multiple centre study on the side effects, effectiveness and reliability of a novel intrathecal treatment strategy by applying anti-Nogo-A antibodies is on the way [7]. Inclusion criteria are acute thoracic SCI motor ASIA A. Twelve patients were treated so far within two weeks without any side effects (personal communication Volker Dietz August 2007).

Drawbacks – critics – fantasy?

SUAW technical concerns: Technical complications required partial/complete removal of the implant system. Technical concerns regarding electrodes and neuroprosthesis have not yet been solved. Neuromedics went bankrupt (April 2000) so that only two instead of ten paraplegics were implanted. Notwithstanding the presentation of MM at the EU in Brussels (March 2000), no prolongation of the grant was achieved although three other paraplegics were already fully prepared for implantation. Press media and TV reports were launched by P. Rabischong to get another EU grant. They attracted world wide attention and raised false hope, unfortunately. Lack of information stopped the trustful SUAW team-work. Misunderstandings and personal interests of some team members were prejudicial to a fruitful, trusty cooperation. In Germany, for example, the rehabilitation physician remained concerned about the reliability, efficacy, and security of the implanted FES system, and about the ethical permission with regard to technical and commercial inspectorate. While he inhibited our surgical activity he became involved in two other SCI projects. In fact, SUAW's reputation is not good and it is too expensive. Moreover, in general rehabilitation, physicians and orthopaedics are not convinced about the need or benefit of voluntary locomotion when paraplegics become independent early in the wheelchair while our two projects need life-long intensive daily physical exercise and an otherwise stable physiological, neurobehavioral condition to follow the training [13, 14].

Regarding CNS-PNS, the scientific concern is mainly about physiology of re-innervation via the first motor neuron despite the experimental data that confirmed the hypothesis of functional restoration of locomotion after two years time [3, 11] and functional results achieved in our first patient (Fig. 4). Unfortunately, fMRI and electroneurophysiological follow-up studies are lacking since the lady refused the examinations. Up to now, rehabilitation physicians and SCI specialists could not be convinced as they simply cannot believe and/or understand the novel physiological concept of plasticity following CNS-PNS connection. We have to accept this concern while we are working hard to come up with our prospective phase 1 study, hopefully early 2008 when we will have an external audit with pre- and postoperative neurological and neurophysiologic follow-up examinations of the patients which are mandatory in this case. However, the five centres in question refused to cooperate as they are not as much interested in restoration of locomotion as they said 2004.

Lay Press Media and TV splashed the SUAW story across the population as to arouse public reports (Stern TV in Germany) and raised hope for the victims to be finally cured as seen from a flow of hundreds of letters and telephone calls – in vain! The first author's personal concern: He was often shown the stick and was confronted worldwide with a square refusal over the last years (Fig. 5).

Concerns stem cell transplantation: The published papers on the clinical use and profit of functioning with the aid of mesenchymal and other kinds of stem cells implantation in paraplegics do not look very serious to us. There is no homogeneous group of patients and no standardized clear assessment of severance of the traumatic spinal cord lesion. Furthermore, to be able to say if stem cells could help and functionally improve a paralyzed SCI patient, we, like others, believe that only an experimental research protocol targeting the same type of cord severance at the same level in animals and human beings in conjunction with an external audit and pre- and postoperative neurophysiological and histological documentation will show the functional validity of the procedure in question.

Concerning the observational study from the largest human experiment in chronic spinal cord injury in China [8] where fetal brain tissue was transplanted into the lesions of more than 400 patients with spinal cord injury (SCI), this was an independent observational study of seven chronic SCI subjects undergoing surgery by Dr. Hongyun Huang in Beijing. Assessments included lesion location by magnetic resonance imaging, protocol of the American Spinal Injury Association (ASIA), change in disability, and detailed history of the perioperative course. Inclusion and exclusion criteria were not clearly defined, as the authors pointed out; subjects with myelopathies graded ASIA A through D and of diverse causes were eligible. In addition, cell injection sites did not always correlate with the level of injury and included even the frontal lobes of a subject with a high cervical lesion. The reason for so-called functional improvement following the procedures might have been transient postoperative hypotonicity that accounted for some physical changes. But no clinically useful sensorimotor, disability, or autonomic improvements could be objectively found. In conclusion, the procedures observed did not attempt to meet international standards for either a safety or efficacy trial. In the absence of a valid clinical trials protocol, the authors stated that physicians should not recommend this procedure to patients.

Conclusions

Restoration of voluntary locomotion in paraplegics is a challenge for multidisciplinary research. Plasticity of the CNS will help to overcome the non-permissiveness of the lesion.

Functional plasticity as it has been demonstrated in our experimental and clinical research projects has never been shown before, when the neuromuscular junctions changed their receptors from cholinergic to glutamatergic and the brain became able to command selected muscles notwithstanding the connection.

Facts

SUAW and CNS-PNS, both experimental clinical projects have demonstrated to enable the paraplegic patient to stand up and to walk again. Patients have to undergo life-long physical exercise training. Best functional results following CNS-PNS connections may be expected within the first year of paraplegia. A trusty multidisciplinary cooperation is a guarantee for the best results.

Fantasy

To convince neuroscientists, even if they are our friends! No new neuroprosthesis implant is on the horizon despite a new team and ongoing announcements. Stem cell transplantation is still in an early experimental stage without clear clinical medical evidence of functional improvement in complete paraplegics after SCI. Intrathecal treatment strategy by applying anti-Nogo-A antibodies raise new hope.

Take home message

Restoration of locomotion in paraplegics after SCI needs a multidisciplinary approach, trusty cooperation and a lot of further experimental research. Reconstructive surgery of spinal cord in paraplegia is no more a fantasy but a fact and challenge for restorative neurosurgeons of ISNR and the WFNS rehabilitation committee.

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Acta Neurochir Suppl (2008) 101: 55–60

Printed in Austria

Posttraumatic rehabilitation and one year outcome following acute traumatic brain injury (TBI): data from the well defined population based German Prospective Study 2000–2002

K. R. H. von Wild, in cooperation with the Hannover, Münster TBI Study Council*

Medical Faculty, Westphälische Wilhelms-University, Münster, Germany

Summary

Follow-up examination to review the one-year outcome of patients after craniocerebral trauma with respect to health related quality of life (QoL) and social reintegration. The data are derived from the prospective controlled, well defined population based, multiple centre study that was performed in Germany for the first time in the years 2000–2001 with emphasis on quality management (structural, process, outcome) and regarding the patient's age, physical troubles, and impaired mental-cognitive, neurobehavioral functioning. TBI severity assessment is according to the Glasgow Coma Scale (GCS) score. Early outcome after rehabilitation is assessed by the Glasgow Outcome Scale (GOS) score of patients following rehabilitation and of 63% of all TBI with the aid of follow-up examination (simplified questionnaire) after one year. Catchment areas are Hanover (industrial) and Münster (more rural) with 2,114 million inhabitants. TBI is diagnosed according to ICD 10 S-02, S-04, S-06, S-07, S-09 with at least two of the following symptoms: dizziness or vomiting; retrograde or anterograde amnesia, impaired consciousness, skull fracture, and/or focal neurological impairment. Within one year 6.783 patients (58% male) were examined in the regional hospitals after acute TBI. The regional TBI incidence regarding hospital admission was 321/100.000 TBI. 28% of patients were <1 to 15 years, 18% >65 years of age. GCS was only assessed in 55% of patients. They were 90.9% mild, 3.9% moderate, and 5.2% severe TBI. A total of 5.221 TBI (= 77%) was hospitalised; 1.4% of them died. Only 258 patients (= 4.9%) of the hospitalized TBI received in-hospital neurorehabilitation (73% male), 68% within one month after injury. They were 10.9% severe, 23.4% moderate, and 65.7 mild TBI. 5% were <16 years, 25% >65 years. One-year follow-up examinations of 4307 individuals (= 63.5% of all TBI) are discussed. A total of 883 patients (= 20.6%) reported posttraumatic troubles, one half were >64 years. One hundred and sixty patients (= 3.8%) could manage their daily life only partly; 75 TBI (= 87.2%) following mild, 5.8% moderate, and 7% severe TBI. One hundred and sixteen patients could not at all manage their activities in training, at school, or in their jobs ($N = 33$ MTBI respectively 54%), 6 (= 10%) moderate, and 22 (= 36%) severe TBI. 2.8% of individuals failed when compared with their pre-traumatic situation. TBI severity, patient's age, concomitant organ lesions, and complications influence health related QoL and early social reintegration.

Keywords: Traumatic brain injury in Germany; quality management of TBI; holistic posttraumatic neurorehabilitation; posttraumatic functional mental-cognitive, neurobehavioral impairment; social reintegration; health related quality of life following TBI.

Introduction

"Brain damage has become synonymous with loss of skills, while the rehabilitation of brain-damaged individuals has become known as a method to restructure lives within a social context" quotation by Anne-Lise Christensen who established the concept of holistic neurorehabilitation after TBI in Europe [3, 5]. Acute traumatic brain injury (TBI) is a major ethical and social burden in the industrialized countries with regard to life-long disability, unnatural death, and the enormous so-

* W. J. Bock, Prof. emeritus Dr. med., former Director of the Neurochirurgische Universitätsklinik, Düsseldorf; W. Gobiet, Dr. med., former Head of the Neurological Clinic, Hessisch Oldendorf; U. Lehmann, Priv. Doz. Dr. med., Senior Registrar at the Department of Accident, Hand, and Restorative Surgery of the Saarland University, Homburg; Saar, K. Mayer, Prof. emeritus. Dr. med., Industrial Cooperative Compensation Fund Accident Clinic, Tübingen; E. Rickels, Prof. Dr. med., Head Department of Neurosurgery, Clinic of the Medical University, Ulm, former Senior Registrar, Neurosurgical Clinic of the Medical University, Hannover (MHH); B. Sens, Dr. Head of the Centre for Quality Management in Healthcare, Physicians' Chamber of Lower Saxony, Hannover; H. D. Wassmann, Prof. Dr., Director of the Neurosurgical University Clinic UKM; Münster, P. Wenzlaff, Medical statistics, Centre for Quality Management in Healthcare, Physicians' Chamber of Lower Saxony, Hannover; R. Wiechers, former Managing Director of the Curatorium CNS for Accident Victims with Injuries of the Central Nervous System and of the Hannelore Kohl Foundation; Bonn, K. R. H. von Wild, Dr. med. Prof. of Neurosurgery, Medical Faculty of the Westphalian Wilhelms-University Münster, Former Head of the Neurosurgical Department and the Unit for Posttraumatic Early Rehabilitation, Clemenshospital, Teaching Hospital, Münster, Germany.

Correspondence: Dr. med. habil. Klaus R. H. von Wild, Medical Faculty, Westphälische Wilhelms-University, Münster, NRW, Frauenburgstrasse 32, D-48155 Münster, Germany.
e-mail: kvw@neurosci.de

cial-economic costs [7, 12]. Modern most efficient, rapid diagnostic procedures by imaging techniques, particularly computed cranial and whole body computerized tomography including reconstruction and thin section procedures, a capable rescue system, state-of-the-art emergency and intensive care treatment [1, 4, 12], new prosperous decompressive neurosurgical procedures in combination with the early neurosurgical neurorehabilitation (ENNR) have enabled increasingly more patients to survive, in many cases, however, suffering from severe impairment of higher cortical functioning (WHO-ICF). Mental-cognitive and neurobehavioral disability calls for a different degree of adjustment than does the need to cope with most physical disabilities [2, 11]. Consequently, neurosurgeons and neurologists with special interest and expertise in acute TBI treatment have become more and more responsible for holistic, multidisciplinary neurorehabilitation [9]. While during the acute posttraumatic phase of treatment the concept of ENNR aims to support spontaneous recovery of impaired brain functioning by preventing secondary and tertiary complications, and so supporting brain plasticity, postacute and long-term rehabilitation is targeted to improve impaired physical and mental-cognitive functioning and the patients' final social reintegration. However, up to now there is little evidence concerning the effectiveness and efficiency of common rehabilitative measures in the sense of evidence based medicine and quality management in respect to the patient's early and long-term outcome and social reintegration [2, 6, 8, 10–12]. Prospective clinical, controlled and multiple centre studies on TBI treatment are lacking. Countrywide studies are impossible for many good reasons. We therefore concentrated on a prospective controlled, well defined population based, multiple centre study in two regions of Germany providing comparable structural and process quality for TBI management regarding the rescue system, the number and kind of hospitals where the patients are admitted and medically treated, and the regional institutions for posttraumatic neurorehabilitation with emphasis on epidemiology, cause of trauma, quality management (structural, process, outcome), and the social-economic costs. Risk factors as they are patient's age, trauma severity, concomitant multiple organ lesions (life threatening polytrauma), acute secondary and postacute tertiary complications, the impact of ENNR and long-term rehabilitation were well investigated with respect to prognosis and one year's functional outcome and health related quality of life. Brief structured interviews were used for the patient's follow-up examination [12]. Ongoing troubles, impairment of mental-cognitive, neurobehavioral functioning with respect to social reintegration are reported.

Patients and methods

The Study Council decided to select the two major regions of Hannover and Münster on the basis of their sound infrastructure as well as their involvement concerning the observance of the guidelines for acute TBI management and of the German Recommendations for ENNR, published in 1993. Both cities have major trauma centres and neurosurgical departments at the medical faculty of the respective universities and at the class A city hospitals, besides another 13 local hospitals each. For posttraumatic rehabilitation 28 institutions are available for both areas. Four special forms (I–IV) have been designed for documentation and computerized analysis by the TBI Study Council. Questionnaires I–III are No I for pre (Ia)- and primary hospital care (Ib), No II Acute hospital treatment, No III for neurorehabilitation, while No IV is for documentation of one-year follow-up, in writing or by telephone call. One-year assessment of the patient's personal situation is by him-/herself and rarely by the relatives regarding personal complaints, functional impairments, restored functioning, disability, social state and leisure time, reemployment, pension, and changes in the patient's life following the trauma within one year. Between March 2000 and February 2001, the study was conducted by collecting the data of all patients admitted to one of the hospitals on the basis of the medical history of having sustained an acute isolated or combined TBI of any kind of severity (GCS 15–3). The definition of acute TBI was made according to the ICD-10 S 02, S 04, S 06, S 07, and S 09 in combination with at least two out of the following complaints: dizziness or vomiting; retrograde or anterograde amnesia; impaired consciousness; skull fracture; and/or focal neurological impairment. The early outcome was evaluated as GOS at the end of hospital medical treatment, at the end of early and after subacute/long-term rehabilitation, social follow-up was by personal examination after one year (Tables 3–8). Data collection was supervised by the Centre of Quality Management in Healthcare and was statistically analyzed by Paul Wenzlaff in close cooperation with the Study Council. The project was evaluated and approved by the Ethical Committee of the Medizinische Hochschule of Hannover, Germany. Data collection was with emphasis on quality management (structural, process, outcome) and analysed according to patient's age, physical troubles, and impaired mental-cognitive, neurobehavioral functioning. TBI severity assessment was according to the Glasgow Coma Scale (GCS) score, early outcome following neurorehabilitation with the aid of the five-point Glasgow Outcome Scale (GOS), and via a simplified questionnaire (document No. IV) during the follow-up examination one year after TBI.

Results

Within one year there were 7010 accidents with TBI regionally documented for the defined population of 2,114,385 which is an incidence for H and MS regions of 332/100,000 population. Taking into account the different regional incidence, it is 268/100,000 in Münster and in Hannover 375/100,000. However, when calculated only for the 6783 completed TBI charts (58% male) following first emergency examination in one of the regional hospitals, the regional incidence for H and MS is 321/100,000 TBI per year. They are 28% individuals <1–15 years and 18% >65 years of age. The mean

Table 1. *Discharge from hospital in regard to GCS*

GCS N	Mild 4.580 87.7%	Moderate 405 7.8%	Severe 9 0.2%	No GCS 227 4.3%	Total N 5.221 100.0%
ICU at first	135	39	168	258	778
Discharge	39.5%	11.4%	59.1%	Intb 178	11.5%
Home with special	3.576	272	2	75	3.925
recommendation	91.1%	6.9%	0.1%	1.9%	57.9%
Home without	695	45	1	8	749
recommendation	92.8%	6.0%	0.1%	1.1%	11.0%
Early neuro-rehabilitation	14	8	2	45	100
	20.3%	11.6%	2.9%	65.2%	1.4%
Early and long only	108	47	2	27	85 = 1.3%
rehabilitation	58.7%	25.5%	1.1%	14.7%	68 = 1.0%

national regional incidence of TBI is 321/100,000: $N = 4643$ Hannover (H), $N = 2140$ TBI Münster (MS). GCS at emergency room was assessed in only 55% of all TBI as 90.9% mild, 3.9% moderate, and 5.2% severe injuries while $N = 3047$ are missing. When retrospectively calculated from the medical findings in the charts (3.9% still missing) they were 86.5% mild, 8.9% moderate and 4.6% severe TBI. Altogether 5221 patients (= 77% of all TBI) were hospitalised, of which 67.8% were in H and 84.9% in MS. Seven hundred and seventy eight individuals (= 14.9%) needed intensive care treatment.

Discharge from hospital (Table 1): data were missing for 32 out of all 5.221 hospitalized patients. Forty-four in-patients died (1.4%). 90% were discharged directly to their home, 3.925 of them with special recommendation for additional medical treatment or diagnostics, 749 patients without any special recommendation. Eighty-six victims were transferred to another hospital, 113 to a nursing home, and 19 for home care. Two hundred and fifty eight patients (= 3.8%) were transferred for neurological-neurosurgical rehabilitation (73% male), 68% of them within the first month after injury, being 5% <16 years, 25% >65 years of age. Early rehabilitation was performed in 100 patients (= 39%) of which one fifth were already referred within the first week. Additional organ lesions were diagnosed in 75% of TBI; they were 30% mild, 42% moderate, and 25% severe TBI lesions. Most frequently (= 40%) were maxillo-facial followed by trivial lesions in 30%, and long bone fractures in 8.4%. GOS at the end of early rehabilitation was 1 = 4%; GOS 2 = 2.7%, 3 = 37.3%, 4 = 26.7%, and 5 = 29.3% while at the end of long-term rehabilitation GOS was 1 = 1.2%, 2 = 1.7%, 3 = 21.8%, 4 = 36.2%, and 5 = 39.1% (Table 2) demonstrating the dynamic process of restoration of functioning over time. Two hundred and thirty

Table 2. *GCS at the beginning of rehabilitation and GOS at time of discharge (N = 258)*

GOS/GCS	Mild	Moderate	Severe	No data	Number
5	39.1%	19.5%		18.1%	26.4%
4	34.8%	29.3%	15.8%	9.6%	24.3%
3	13.0%	31.7%	52.6%		14.7%
2			15.8%		1.2%
1		2.4%	5.3%		0.8%
Missing	13.1%	17.1%	10.5%	72.3%	32.6%
Total number	115	41	19	83	258
%	100.0%	100.0%	100.0%	100.0%	100.0%

nine patients (= 93.4%) were mobilized. Fifteen patients showed muscle contractors; seven patients had single bed pressure and altogether 2.9% single and multiple pressure sores. A total of 102 patients were able to take care of themselves at the time of discharge, 18 of these patients (= 17.6%) being older 65 years. There were 41 of 95 polytraumatized patients able to take care of themselves at the time of discharge, while 21 patients needed home care, nine a nursing home, and 13 were transferred to another hospital. Two patients received sheltered work. Nine patients were provided support from another social institution. Following "mild" TBI 40% of patients were discharged home, able to take care of themselves. One third of the "moderate" TBI patients were dismissed taking care of themselves or else transferred to another hospital. One third of patients following "severe" TBI were also transferred to another hospital or to a nursing home.

Half of the 26 patients transferred to a nursing home, but only 22% of the 54 patients discharged for home care were >65 years. Adjuvants were provided for 87 patients (= 34.1% of 255 patients discharged from rehabilitation). Fifty-eight of these patients answered the questionnaire. Of one-year follow-up examination: 42 patients were using special adjuvants after one year. Neurological state: One patient (= 0.5%) showed paresis

of the lower limbs. Fifty patients complained of visual disturbances (19.4%). Amaurosis was diagnosed in six of the patients (=2.4%), in four patients one side, in two patients complete loss of vision. No patient was deaf on one or both sides. Concerning further treatment on an outpatient basis physiotherapy was recommended in 85%, vocational therapy in 53.4%, speech/language therapy in 27.4%, neurological pedagogic exercises in 25.6%, neuropsychological therapy in 42.3% and special PC-based mental-cognitive training in 12.2%. The prognosis for social and vocational reintegration at the time of discharge was said to be as follows for 258 patients: 13.2% of patients to be employed as before; 14.3% to require vocational support, 8.5% to be employed with some restriction, unemployed 4.7%, and incapable of earning their own living 9.3%; 27% did not meet the criteria because of prior pension and 7% because of previous unemployment; 1.9% may go back to school; 1.6% will go back to school but will have to repeat the class; 0.4% will need a school for handicapped pupils, and 1.2% of patients will not be able to go back to school, unknown prognosis for 9.3%; three patients died during rehabilitation.

Completed one-year follow-up questionnaires were available for two thirds of TBI (4307 individuals = 63.5%). They were 14% children <6 yrs, 16% children and adolescents between 6 and 18 yrs, 53% adults between 17 and 64 yrs, and 15% >65 yrs of age. Concerning TBI severity there is no difference between the responding and the non-responding cohort. One year after the accident mortality was 4.7% (212 patients out of 6783 TBI). Of the 212 documented cases of death, 19 patients (=0.2%) died after hospital admission during initial emergency treatment, 44 TBI (=0.6%) during hospital care, three patients (=0.04%) during posttraumatic rehabilitation, six patients due to their TBI after discharge, 51 patients for other reasons, and 89 patients of unknown reasons after their discharge.

One year after trauma 20.6% out of 99.4% TBI responded to the question about their posttraumatic complaints of adverse effects (Table 3). Remarkable is the percentage of about 50% with troubles in the advanced age group (Tables 4 and 5). With regard to TBI severity they were 90% after mild, 4.6% each after moderate and severe TBI. Specifications are listed in the tables below.

When analyzing the long-term outcome of 240 TBI patients, there were 66% severe, 23% moderate, and 11% mild injuries, 32% achieved GOS 5, 27% GOS 4, and 32% were only GOS 3. With reference to initial GCS, 16% of the severe, 27% of the moderate, and 33% of the mild TBI were reintegrated into their former social activities and profession without any restrictions. One hundred and forty five are staying with their families (Table 6). About one half (=58%) of the patients underwent some kind of outpatient rehabilitation. However, neuropsychological training was restricted to only 7% of all patients reviewed. This significant gap between high-impact clinical medicine on the one side

Table 3. *One-year follow-up: TBI related complaints related to patients' age one year after TBI. N = 883 (= 20.6%) out of 4.283 TBI Respondents (= 99.4%)*

Complaints as a sequel of injury	Less than 6 yrs	6–16 yrs	17–64 yrs	65 yrs and older	Total
Yes	2.0%	7.8%	22.6%	47.3%	20.6%
N = total	594	795	2.268	626	4.283

Table 4. *Nature of troubles one year after TBI as to patients' age (N = 872) Multiple answer options*

Age (yrs) Troubles	<6 N = 26	6–15 N = 61	16–64 N = 500	≥65 N = 285	Total N = 872
Headache	23.1%	54.1%	59.6%	62.8%	59.5%
Dizziness	7.7%	19.7%	29.2%	62.8%	39.2%
Impaired Concentration	11.5%	26.2%	36.0%	49.7%	39.3%
Impaired mobility	3.8%	13.1%	18.4%	22.8%	19.2%

Table 5. *Complaints one year after TBI relating to patients' age (N = 872)*

	<6	6–15	16–64	>65	Total
Speech impairments	3.8%	13.1%	5.6%	6.2%	6.3%
Impaired vision	7.7%	8.2%	8.2%	10.7%	9.1%
Impaired hearing		3.3%	6.0%	12.1%	7.7%
Impaired sense of smell	3.8%	8.2%	8.4%	5.2%	7.2%
Other complaints	11.5%	32.8%	28.0%	11.4%	22.5%

Table 6. *Changes in the living situation related to patient's age (multiple-answers option) 5 severe TBI and 10 MTBI are living in a (nursing) home*

Age (yrs)/situation	<6	6–16	17–64	>65	Total
Home/nursing home			7	23	30
			6.4%	21.1%	27.5%
In a care home			2	10	12
			1.8%	9.2%	11.0%
With relatives/partners	1	3	24	9	37
	0.9%	2.8%	22.0%	8.3%	33.9%
Alone/independent			21	6	27
			19.3%	5.5%	24.8%
Other	2	1	2	3	8
	1.8%	0.9%	1.8%	2.8%	7.3%

Table 7. *Self-assessment of coping with daily life (N = 4.200)*

Coping with everyday life	<6 yrs	6–16 yrs	17–64 yrs	>65 yrs	Total
No difference	528	783	2.153	459	3.923
	99.2%	98.9%	95.1%	75.0%	93.4%
Partly the same		1	57	102	160
		0.1%	2.5%	16.7%	3.8%
Not at all the same	4	8	54	51	117
	0.8%	1.0%	2.4%	8.3%	2.8%
Total	532	792	2.264	612	4.200

Table 8. *Coping with training/school/profession related to the pre-event situation (N = 3.533) Only 116 patients cannot at all manage their social activities: 33 MTBI (= 54%), 6 (= 10%) moderate, 22 (= 36%)*

Training/school/ profession	<6 yrs	6–16 yrs	17–64 yrs	>65 yrs	Total
No difference	396	764	1.975	195	3.330
	98.0%	97.2%	93.4%	85.5%	94.3%
Partly the same		13	66	7	87
	0.2%	1.7%	3.1%	3.1%	2.5%
Not at all the same	7	9	74	26	116
	1.8%	1.1%	3.5%	11.4%	3.3%
Total	532	792	2.264	612	4.200

and a deficient outpatient treatment on the other has been reconfirmed in our prospective study. 80% of the interviewed patients report their personal situation as being unchanged, 8% worse, 2% severely worse, with data lacking in 10% of all the patients. Complaints following TBI were reported in 21% of patients. Six victims were still in the rehabilitative process. We analyzed the answers from 46 of 64 patients who had previously received vocational therapy. Sixteen patients (34.0%) were reemployed but are not able to function as well on their jobs or in daily life as they did before their injury; 27% stopped working or changed their job, and ten patients still received vocational therapy (Tables 7, 8).

A special form of neurological pedagogic exercise and/or neuropsychology was applied in 214 patients, 146 patients (= 68.2%) responded to our questionnaire. Altogether only 13 patients (= 8.9%) received regular neuropsychological treatment.

Discussion

Neurorehabilitation aims at restoration of impaired higher cortical functioning and is targeted at final social reintegration after brain damage. Holistic rehabilitation is an ongoing chain that has to be followed over many years [3, 5]. Functional rehabilitation is an original task of neurosurgery. According to the WHO-ICF definitions functioning is used as an umbrella term encompassing all body functions, activities and social participation. Impairments refer to loss of structures and functions while disabilities mean difficulty in functioning at the body or societal levels, in one or more life domains, as experienced by an individual with a health condition in interaction with contextual factors according to definition (WHO in 2006).

Over the last two decades it has been demonstrated that neurorehabilitation like neurotrauma care depends on a multidisciplinary team approach. Also one has to admit that up to now there is little hard evidence for a causal relationship between the proposed mechanisms of recovery of functions following TBI and the effects of neurorehabilitation interventions [6, 8]. With reference to D. Stein [10] there is considerable disagreement as to what might be the most appropriate approach to studying and manipulating injury-induced CNS plasticity. We believe that it is now more likely that restoration of functioning of what is attributed to recovery of functions is really compensation or substitution of function initiated by cerebral trauma over time. In the field of neurorehabilitation the term "recovery of functioning" is generally taken to describe that sensory, motor, and cognitive neurobehavioral impairments that follow TBI are reduced or eliminated without necessarily specifying how such deficits are reduced or eliminated. Considering a strictly phenomenological definition, recovery can be taken to imply that post-injury functioning is the same as that seen prior to the injury when there is no causal set of physiological mechanisms proposed to account for functional changes. Another problem that might occur is that the extent to which deficits are reduced in order to claim recovery is not always clearly specified. What is expected of the patient by himself, his relatives, and the doctors and therapists may vary considerably, depending on who holds the expectations and who sets the criteria for determining what is and what is not recovery [3, 5].

This is also true for assessing the patients' health related quality of life after TBI [2]. Our interview one year after the trauma was focused on the patients' physical and cognitive complaints and social reintegration. The early outcome at the end of neurorehabilitation and after one year was as good as we expected, fully justifying our concept for ENNR as well as the enormous costs involved [9, 12]. About one half (= 58%) of the patients underwent some kind of outpatient rehabilitation. However, long-term neuropsychological therapy was restricted to only 7% of all patients reviewed. This

significant gap between high-impact clinical medicine on the one side and a deficient outpatient treatment on the other has been reconfirmed in our prospective study. The patients' data of their social outcome, as it was self-assessed one year after the traumatic event, provide new information regarding social reintegration and leisure-time activities one year on. 80% of the interviewed patients report their personal situation as being unchanged, 8% worse, 2% severely worse, with data lacking in 10% of all the patients.

TBI severity and the patients' ages as strong prognostic factors are in accordance with the one year follow-up findings. At present our international task force on quality of life after brain injury (abbreviation, QOLIBRI) chaired by Jean-Luc Truelle, Paris, and Nicole von Steinbüchel, Göttingen [11], is going to publish the new concept and its first clinical data of the novel life-assessment instrument, called The QOLIBRI, successfully set up over the past eight years. It was translated into several international languages including English, Spanish, Arabic, Taiwanese, Mandarin, and Japanese. Its reliability and efficacy has been tested and methodically proven in more than 1500 adult individuals following TBI in different countries under the leadership of N. von Steinbüchel. This tool will represent the patient's metadimension beyond the handicap by covering six domains (physical, cognitive, psychological, functional, social, and personal) with a five-point scoring system.

Conclusion

Quality management of TBI in Germany is performed at a high standard. Notwithstanding, neuropsychological in- and out-patient treatment to help restoring of frequently impaired mental-cognitive functioning and so the victim's final social reintegration and quality of life is still underestimated for head trauma care in both H and MS regions that were analysed. The one-year outcome data underline the efficiency of the German social and health care systems. This study provides new information on TBI quality management that could also be used for education and training.

Acknowledgement

The study was granted by Kuratorium ZNS and Hannelore Kohl donation, Bonn, Cerebprotect, Förderverein für traumatologische Frührehabilitation eV, Münster, Germany World Federation of Neurology Research and Education Foundation, Winston-Salem, NC, USA.

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Acta Neurochir Suppl (2008) 101: 61–64

Printed in Austria

A randomized controlled trial of constraint-induced movement therapy after stroke

K.-C. Lin[1], C.-Y. Wu[2], J.-S. Liu[3]

[1] School of Occupational Therapy, College of Medicine, National Taiwan University, and Division of Occupational Therapy, Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital, Taipei, Taiwan
[2] Department of Occupational Therapy, Chang Gung University, Taoyuan, Taiwan
[3] Department of Medical Education and Department of Surgery, Cathay General Hospital, Taipei, Taiwan

Summary

Objectives. To evaluate the benefits of constraint-induced movement therapy (CIMT) relative to traditional intervention equal in treatment intensity and use of restraint mitt outside rehabilitation on motor performance and daily functions in stroke patients.

Design. Two-group randomized controlled trial (RCT).

Setting. Rehabilitation clinics.

Subjects. Twenty-two chronic stroke patients (mean time postonset of stroke = 18.9 months).

Intervention. The subjects were randomized to receive CIMT (restraint of the less affected limb combined with intensive training of the affected limb) or traditional intervention (control treatment) during the study. The treatment intensity was matched between the two groups (2 h/d, 5d/wk for 3 wk). Both groups of patients received restraint of the less affected limb outside rehabilitation (ca. 3 h/d).

Main measures. Motor performance was evaluated using the Fugl-Myer Assessment and the Motor Activity Log. Functional outcomes were evaluated using the Functional Independence Measure and the Nottingham extended activities of daily living scale.

Results. The CIMT group showed significantly greater improvements in motor performance, level of functional independence, and the mobility domain of extended activities of daily living.

Conclusions. This is the first RCT to show the benefits of CIMT, relative to control treatment equal in amount of therapy, in improving motor performance and some aspects of basic and extended activities of daily living.

Keywords: Controlled clinical trials; occupational therapy; rehabilitation; stroke; functional outcomes.

Introduction

Up to 85% of stroke survivors experience impairment of upper limb movement, leading to permanent dependency on community care [10]. Constraint-induced movement therapy (CIMT) has been advocated to remediate upper limb impairment and functional ability. CIMT involves restraint of the less affected limb for an extended period and intense functionally oriented task practice of the affected limb [2, 8, 10].

Numerous studies [2, 8, 10] in stroke patients have shown that, in comparison with traditional intervention, CIMT can improve motor performance and functional use of the affected limb. However, a major concern about efficacy of CIMT is the lack of a study with an equal intensity control group [8]. CIMT involves training of the affected limb by shaping for several hour(s) per day over consecutive weeks while constraining use of the less affected upper extremity (UE) outside treatment sessions during this period to induce increased use of the affected limb. In contrast, traditional intervention involved training matched in the hours of training to the CIMT group but not in mitt use. The CIMT group arguably received more "treatment" during restraint wear outside rehabilitation, a possible confounding factor in previous research.

Previous research has studied the effects of CIMT on self-care ability or basic activities of daily living (ADL) performance. This study extended previous research by studying treatment outcomes in basic and extended ADL performance by using an equal intensity control group. We hypothesized that, compared to traditional intervention, CIMT would produce beneficial effects on movement performance and functional outcomes.

Correspondence: Dr. Ching-yi Wu, Department of Occupational Therapy, Chang Gung University, 259 Wen-hwa 1st Road Kwei-shan, Taoyuan 333, Taiwan. e-mail: cywu@mail.cgu.edu.tw

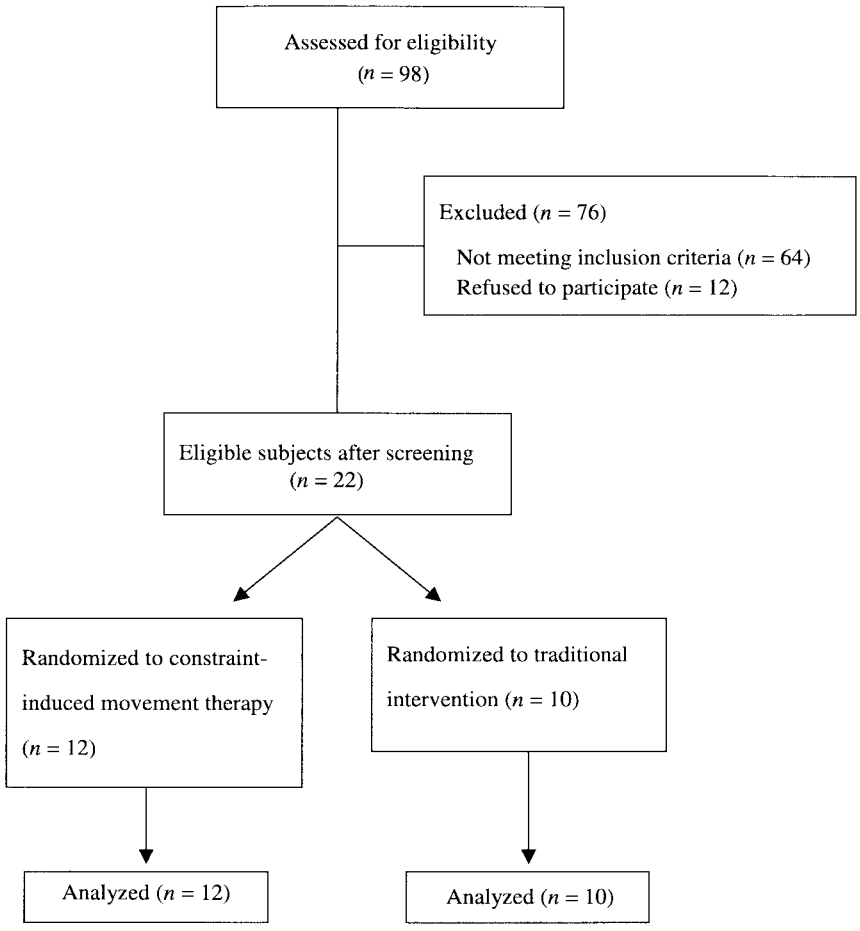

Fig. 1. Flow diagram of the randomization procedure

Materials and methods

Twenty-two subjects with a first-ever stroke consented to participate in this study. The inclusion criteria were: 1) able to reach Brunnstrom stage III or above for the proximal part of UE [9], 2) considerable nonuse of the more affected UE (amount-of-use score < 2.5 on the motor activity log) [7], and 3) the ability to understand and follow instructions.

Outcome measures

The outcome measures included Fugl-Meyer Assessment (FMA) [3], Functional Independence Measure (FIM) [5], Motor Activity Log (MAL) [7], and the Nottingham Extended ADL Scale (NEADL) [4], demonstrating good reliability and validity. FMA (maximum optimal score 66) was used to assess motor impairments and FIM (maximum optimal score 126) to objectively measure changes in ADL function. The MAL was used to measure perceived functional use of the affected limb including amount of use in the affected limb (AOU) and quality of movement (QOM) (score range 0–5 for both). The NEADL (maximum score 22) evaluated extended ADL abilities.

Design and intervention

A randomized pretest and posttest control group design was applied. Before and after the 3-week intervention period, the tests were administered by a blinded rater.

The subjects in both groups received individualized, 2 h therapy sessions, 5 times/week for 3 weeks and were required to place the less affected hands and wrists in mitts with velcro straps every weekday for three hours. The only difference between these two groups lied in the treatment programs during the 2 h session. The CIMT group focused on the functional training of the affected limb (e.g., turning on and off a light switch or picking up a hairbrush and combing hair). The traditional intervention group focused on neurodevelopmental techniques, as well as weight bearing with the affected limb and fine motor dexterity activities.

Statistical analysis

For all variables, analyses of covariance (ANCOVAs) were used to examine the effects of CIMT vs. traditional intervention. The pretest performance and restraint time per day were the covariates, group was the independent variable, and posttest performance was the dependent variable. Effects sizes were calculated for each variable and indexed by the effect size r [1].

Results

The demographic (gender and age) and clinical (side of lesion, months after stroke, Brunnstrom stage of proximal part of upper limb, and daily restraint hours) characteristics of subjects in the two groups (12 subjects in the CIMT group and 10 in the traditional intervention group) were comparable.

Table 1. *Descriptive and inferential statistics on the outcome measures*

	Pretreatment (mean ± SD)		Posttreatment (mean ± SD)		ANCOVA		
	CIMT ($n = 12$)	TI ($n = 10$)	CIMT ($n = 12$)	TI ($n = 10$)	F (1, 18)	P-values	Effect size r*
FMA (UE)	45.67 ± 7.87	54.60 ± 9.57	52.42 ± 6.69	57.90 ± 9.63	3.91	0.03	0.41
FIM	118.00 ± 9.94	118.90 ± 11.62	122.17 ± 6.56	119.00 ± 10.54	12.57	<0.010	0.64
Self-care	38.08 ± 2.98	36.50 ± 9.35	39.58 ± 3.99	36.60 ± 9.05	6.05	0.012	0.50
Sphincter	14.00 ± 0.00	14.00 ± 0.00	14.00 ± 0.00	14.00 ± 0.00	0.00	0.50	0.00
Transfer	20.25 ± 1.76	20.70 ± 0.95	21.00 ± 0.00	21.00 ± 0.00	0.00	0.50	0.00
Locomotion	12.50 ± 1.45	13.20 ± 2.53	13.50 ± 0.67	12.90 ± 2.51	8.89	<0.010	0.57
Communication	13.50 ± 1.24	13.80 ± 0.63	13.67 ± 1.15	13.80 ± 0.63	0.47	0.25	0.16
Social cognition	19.67 ± 3.77	20.70 ± 0.95	20.42 ± 2.02	20.70 ± 0.95	1.78	0.10	0.30
MAL							
AOU	0.78 ± 0.78	1.33 ± 0.69	1.41 ± 0.53	2.30 ± 0.95	2.90	0.053	0.37
QOM	0.64 ± 0.40	1.53 ± 0.89	1.69 ± 0.59	2.52 ± 0.96	0.002	0.48	0.01
NEADL**	26.09 ± 11.99	28.50 ± 14.68	29.36 ± 10.90	28.20 ± 15.63	2.30	0.075	0.35
Mobility**	11.64 ± 4.54	12.70 ± 6.13	12.91 ± 4.32	11.30 ± 6.68	4.14	0.030	0.44
Kitchen**	5.91 ± 4.48	4.40 ± 3.24	6.18 ± 4.21	4.50 ± 3.54	0.06	0.41	0.06
Living affairs**	3.55 ± 3.27	5.30 ± 5.27	4.09 ± 3.86	5.70 ± 4.57	0.22	0.67	−0.11
Leisure**	6.18 ± 2.44	6.70 ± 3.40	5.00 ± 3.55	6.10 ± 3.18	0.003	0.48	0.00

* According to Cohen [1], a large effect is represented by an r of at least 0.50, a moderate effect by 0.30, and a small effect by 0.10. A positive value of effect size indicates the effect is in the hypothesized direction and a negative value indicates the effect is opposite to the hypothesized direction.
** The denominator degree of freedom for the F tests was 17 because the data of the NEADL in one subject of the CIMT group were missing.
ANCOVA Analysis of covariance; *CIMT* Constraint-induced movement therapy; *TI* Traditional intervention; *FMA* Fugl-Meyer Assessment; *UE* Upper extremity; *FIM* Functional Independence Measure; *MAL* Motor Activity Log; *AOU* Amount of use; *QOM* Quality of movement; *NEADL* Nottingham Extended Activities of Daily Living.

The results showed significant and moderate-to-large effects in favor of the CIMT group on the FMA and two domains of the FIM (i.e., self-care and locomotion) (Table 1). Nonsignificant and small-to-moderate effects were found in the subtests (AOU and QOM) of the MAL. A significant and moderate effect was found in the domain of mobility on the NEADL in favor of CIMT but not in other domains.

Discussion

Consistent in part with the a priori hypothesis, the CIMT group reduced motor impairment to a greater extent, measured by the FMA, and induced greater gains in functional capacity, especially on the aspects of self-care and locomotion, as measured by the FIM.

The findings on the FMA and FIM are consistent with previous studies [2, 10]. In comparison with previous studies, our study provided more compelling evidence that patients in the CIMT group were able to show better motor performance at the impairment level and functional capacity than the traditional intervention patients. The previous studies employed the control group with equal treatment hours in the clinic as the CIMT group whereas the present study required both groups to receive equal treatment hours in the clinic and restraint time outside rehabilitation. The only difference between the two groups is the treatment methods during the 2 h training in the clinic. The CIMT protocol emphasized intensive practice and use of functional tasks to train the affected arm, which might provide sufficient proprioceptive and visual feedback to develop the internal models for sound control of movement [6].

Inconsistent with previous studies [8, 10] and the hypotheses, there were no significant between-group differences in the scores of MAL. The possible reason is that this study employed the restraint of the less affected limb in the control group which may have enhanced the spontaneous use of the affected limb. There were no significant differences in the overall score of the NEADL possibly because the CIMT program did not involve household or leisure tasks. However, the CIMT group exhibited significantly greater improvements in the mobility domain of the NEADL. These improvements might result from enhanced performance of the upper limb important for a variety of functional mobility.

This study is unique to have used a control group equal in amount of treatment hours. Given the small contrast between the two groups, the findings suggest the robust effects of intensive training of the affected hand. Future research may enroll a larger sample with individual-based restraint time for follow-up study to evaluate the long-term benefits of CIMT on extended

ADL, work and reintegration to community, and stroke-related quality of life.

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Acta Neurochir Suppl (2008) 101: 65–70

Printed in Austria

Increased regional cerebral perfusion in contralateral motor and somatosensory areas after median nerve stimulation therapy

J.-T. Liu[1], J.-K. Lee[2], P.-J. Chang[2], C.-M. Sun[2]

[1] Department of Neurosurgery, Chung Shan Medical University Hospital, Taichung, Taiwan
[2] Department of Nuclear Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan

Summary

Objective. To evaluate change in regional cerebral perfusion (rCBF) after median nerve stimulation (MNS) therapy in brain-damaged patients.

Methods. Twelve brain-damaged patients received 12 courses of MNS. Technetium-99m-ethyl cysteinate diethylester (^{99m}Tc-ECD) SPECT was performed before and 4 weeks after MNS initiation. Clinical response was assessed by Glasglow coma scale or clinical improvement. 12 MNS patients were grouped as good responder (GR) ($n = 6$) and poor responder (PR) ($n = 6$) according to therapy response. Scan images were analyzed by Statistical Parametric Mapping 2 (SPM2).

Results. In the GR group, paired Student t test between the pre- and post-MNS images showed 2 activation clusters over the left frontal and parietal lobes, including regions of the precentral gyrus, middle frontal gyrus, superior frontal gyrus, subgyral, inferior parietal lobule, and postcentral gyrus (corresponding to Brodmann areas 4, 6, and 40). In the PR group, paired Student t test did not show any activation clusters. Clusters with significant differences between the GR and PR groups shared no mutual voxels with those clusters having significant regional effects after MNS in the GR group.

Conclusions. Median nerve stimulation enhanced the rCBF of the contralateral motor and somatosensory cortex, which is compatible with the few previous studies using other modalities.

Keywords: Median nerve stimulation (MNS); regional cerebral perfusion (rCBF); tomography; emission-computed; single-photon (SPECT); technetium; technetium-99m-ethyl cysteinate diethylester (^{99m}Tc-ECD).

Introduction

During the past two decades, neuroanatomical and neurophysiological studies in animals, and neurophysiological and neuroimaging studies in humans have demonstrated that the adult brain is capable of extensive functional recovery. The adult brain maintains the ability for reorganization or plasticity in response to various external factors, including peripheral nerve injury and stimulation, motor performance, and focal lesions of the sensorimotor cortex [1, 2]. Electrical stimulation has been used for pain management, brain injury, and coma. The mechanisms underlying the efficacy of this modality are poorly understood. Recent studies have employed functional imaging to investigations of brain responses to median nerve stimulation. These studies suggest responses in sensorimotor regions [3, 4].

Right median nerve stimulation affects the left side of the brain, with the electricity stimulating various areas. Evoked potential studies propose that this peripheral stimulus travels ipsilaterally in the posterior column of spinal cord to the dorsal column nuclei at the cervicomedullary level, then the signal crosses to the contralateral thalamus, and then stimulates the frontoparietal sensorimotor cortex [5–9]. Cerebral blood flow is reduced in stroke [10] and brain-injured patients [6]. Increased regional cerebral perfusion in these patients would be of clinical significance.

To the best of our knowledge, there is no other previously published study involving a voxel-wise analysis of regional cerebral perfusion (rCBF) following median nerve stimulation (MNS) therapy and the relationship of this activation to the presence of absence of clinical response. This retrospective study evaluates the change in rCBF after 4 weeks of MNS in brain-damaged patients, and examines the correlation between rCBF change and clinical effectiveness of MNS therapy.

Materials and methods

Patient selection

From April 2003 to October 2005, a total of 13 sessions of right-side median nerve stimulation (MNS) therapy was administered in 12

Correspondence: Chen-Ming Sun, M.D., Department of Nuclear Medicine, Chung Shan Medical University Hospital, 110 Sect. 1, Chen-Kuo N Road, Taichung City, Taiwan. e-mail: sunchenming@yahoo.com

Table 1. *Clinical characteristics of brain-injured patients receiving MNS*

	Age	Sex	Cause of brain damage	Duration of brain damage (months)	Pre-MNS GCS	Post-MNS GCS
Good responder group						
1	24	M	head injury	38	E4M5V2	E4M6V2
2	21	M	head injury	6	E3M4Vt	E4M4Vt*
3	20	F	head injury	2	E3V2M5	E3V4M6
4	78	M	left carotid artery stenosis	6	E4M6V2	E4M6V2* less frequent headache
5	41	F	head injury	3	E3M3Vt	E3M4Vt
6	27	M	head injury	11	E4M4Vt	E4M5Vt
Poor responder group						
1	18	M	head injury	2	E1M1V1	E1M1V1
2	24	M	head injury	6	E4M2Vt	E4M2Vt
3	19	M	head injury	4	E2M4Vt	E2M4Vt
4	51	M	head injury	24	E1M4Vt	E1M4Vt
5	26	M	head injury	2	E4M2Vt	E4M2Vt
6	22	F	head injury	7	E4M2Vt	E4M2Vt

* Vt: Glasgow Coma Score for verbal could not be assessed due to tracheostomy.

patients (9 males and 3 females with an age range from 18 to 78 years). Eleven patients suffered from traumatic brain injury (all due to motor vehicle accident) and had disturbed consciousness. (The duration of disturbed consciousness ranged from 2 to 38 months.) One patient with clear consciousness suffered from left carotid artery stenosis, and he complained of chronic headache. Inclusion criterion for this study was brain damage resultant from trauma or cerebral vascular disease. Informed consent was obtained from all of the patients. Patients received scans before and 4 weeks after medial nerve stimulation treatment. All of the patients received one session of medial nerve stimulation therapy administered by the same operator. Therefore, the second session of medial nerve stimulation required in one of the patients was omitted from the study. The MNS therapy lasted for at least 4 weeks. The patients' clinical features are summarized in Table 1.

Stimulation technique and imaging

Technetium-99m-ethyl cysteinate diethylester (^{99m}Tc-ECD) single-photon emission tomography (SPECT) scans were performed twice, once before and once after each MNS therapy. The interval between the last stimulation session and post-MNS SPECT scan was less than 14 h. In accordance with study parameters, a total of 24 SPECT scans (12 pre-MNS and 12 post-MNS) were administered. The ^{99m}Tc-ECD was labeled and reconstituted using the Neurolite® kit (Du Pont Merck Pharmaceutical Company, Billerica, MA) in accordance with the product instructions. The radiopharmaceutical dose injected was approximately 20 mCi (740 MBq) for all studies. Using an identical protocol for both studies, the SPECT images were acquired with the same scanner within 1 to 2 h of the radiopharmaceutical injection. The data were acquired in a 128×128 byte matrix. Data sets were acquired at 3° intervals for 35 seconds each, with a total of 40 sets (120° per camera head). The imaging resolution was 8 to 9 mm. Images were reconstructed using a standard filtered back projection algorithm.

The MNS was performed with a Focus® electric stimulator (Empi, Inc., St Paul, MN). A transcutaneous electric stimulator pasted on the palmar side of the right wrist skin supplied trains of asymmetric biphasic pulses at an amplitude of 20 mA with a pulse width of 300 micro-second at 35 Hz for 20 seconds on and 50 seconds off. The stimulation time was 10 h (7 to 11 a.m. and 1 to 7 p.m.) per day applied to a comatose patient. The stimulation time was 8 h (7 to 11 a.m. and 2 to 6 p.m.) applied to a conscious patient or when any comatose patient became conscious. The stimulation period between the pre- and post-MNS SPECT scans was at least 4 weeks.

Therapy response was assessed by Glasglow coma scale (GCS) or clinical improvement according to medical records. Twelve MNS therapies were grouped as good responder (GR) ($n = 6$) and poor responder (PR) ($n = 6$) according to therapy response. The GR group was comprised of 6 MNS patients, of these, 5 showed improvement of GCS, and one (the left carotid artery stenosis patient) showed alleviation of symptoms (less frequent headache). The PR group was comprised of 6 MNS patients without either GCS or clinical improvement.

All images were spatially normalized onto the stereotactic coordinate system of Talairach and Tournoux atlas by SPM2 (Wellcome Department of Cognitive Neurology, London) under Matlab® (The Maths Works Inc., Natick, MA) with a template image provided by SPM2 package. The stereotactically normalized images (dimensions: $x = 79$, $y = 95$, $z = 69$; voxel size: $2 \times 2 \times 2$ mm) were then smoothed by three-dimensional convolution with an isotropic Gaussian kernel (FWHM: 12 mm). These images were adjusted for scan-to-scan differences in global flow by scaling the voxel values for each scan to the mean (proportionally scaling the global flow to a physiologically realistic value of 50 ml/dl/min). Threshold masking of the images was completed by masking out all scans voxels that fail to reach 80% of the mean global value to ensure that only grey-matter voxels were included in the analysis [11–14].

Statistical analysis

Commercially available SPSS 11.5 statistical software (SPSS Inc., Chicago, IL) was used to analyze the patient data. The statistical calculations produced a statistical map of t-values within the image volume. To compare the differences between GR and PR groups, a two-sided two-sample t-test was performed. The voxel-level threshold was set to $p < 0.001$ on each side uncorrected for multiple comparisons, and the cluster-level was set to $p < 0.001$ on each side corrected for multiple comparisons by family-wise error rate algorithms.

The corresponding anatomical region of each local maximum was derived by Talairach daemon client 1.1 software (The Research Imaging Center, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA), which is a Web-based application that returns anatomic and Brodmann area information based on the 1988 Talairach and Tournoux atlas coordinates. This is a widely used application for determining Brodmann areas based on surviving areas of activation.

Results

Of the GR group, paired Student t-test between the pre- and post-MNS images showed significant regional increases in rCBF after MNS in 2 activation clusters (cluster sizes were 272 and 102 voxels, respectively) over the left frontal and parietal lobes, including the regions of the precentral gyrus, middle frontal gyrus, superior frontal gyrus, subgyral, inferior parietal lobule, and postcentral gyrus (corresponding to part of the Brodmann areas 4, 6, and 40), when significance (height) thresholds were set at voxel-level $p < 0.001$ uncorrected for multiple

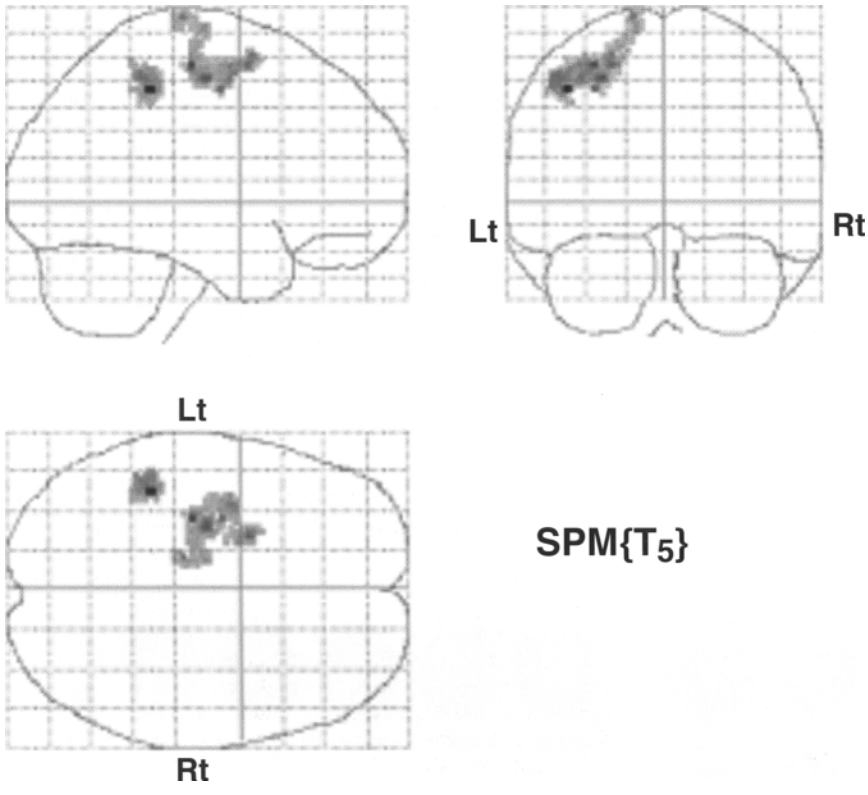

Fig. 1. Regional cerebral perfusion is significantly increased in the good responder group after MNS therapy. Two clusters with significantly increased regional cerebral perfusion are shown in the maximum projection images (glass brain) in the transaxial, coronal, and sagittal views. *Lt* left, *Rt* right

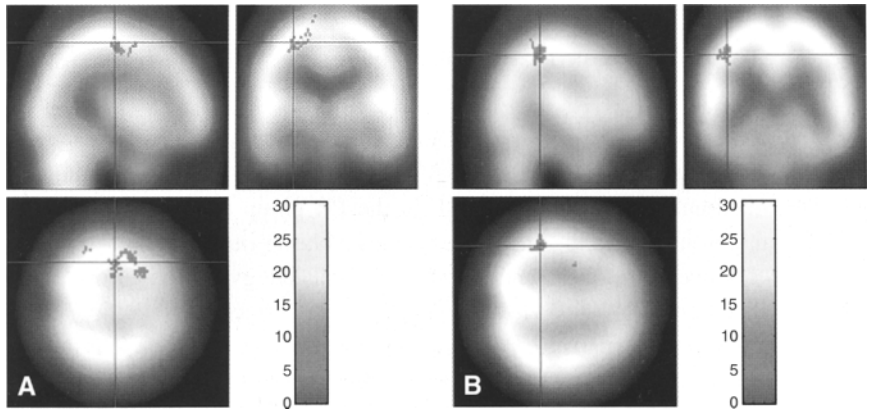

Fig. 2. A statistically significant regional cerebral perfusion increase is seen in the good responder group after MNS therapy. Two clusters of significantly increased regional cerebral perfusion are overlaid on the mean image (in inverse gray scale) of the spatially normalized and smoothed SPECT images of all patients. (A) Cluster with 272 voxels. (B) Cluster with 102 voxels

Table 2. *Statistical analysis of activated clusters by cluster level, voxel level, and montreal neurological institute coordinates*

Cluster-level			Voxel-level				MNI coordinate[1] (mm)		
$P_{corrected}$	k_E(Voxel)[3]	$P_{uncorrected}$[4]	$P_{corrected}$[5]	T	(Z)	$P_{uncorrected}$	x^2	y^2	z^2
<0.001	272	<0.001	0.898	18.19	4.43	<0.001	−30	−20	58
			1.000	16.32	4.32	<0.001	−26	−14	52
			1.000	13.36	4.10	<0.001	−22	4	58
<0.001	102	<0.001	0.070	30.43	4.96	<0.001	−42	−38	48
			1.000	7.11	3.33	<0.001	−40	−44	58

[1] *MNI* Montreal Neurological Institute coordinate of local maxima (more than 8.0 mm apart) in each cluster (x, y, z).
[2] x, y, z Talairach and Tournoux coordinate.
[3] k_E Size.
[4] $P_{uncorrected}$ P value uncorrected for multiple comparison.
[5] $P_{corrected}$ P value corrected for multiple comparison by family-wise error rate algorithms.

Table 3. *Anatomical location of local maxima (>8.0 mm apart) shown as montreal neurological institute coordinates, talairach and tournoux coordinate, and corresponding anatomical region*

Cluster	MNI[1] coordinate			Talairach and tournoux coordinate (*x*, *y*, *z*)			Corresponding anatomical location of local maxima[2]
	x	*y*	*z*	*x*	*y*	*z*	
Cluster 1	−30	−20	58	−30	−17	54	left frontal lobe, precentral gyrus, Brodmann area 4,
(272 voxels)	−26	−14	52	−26	−11	48	left frontal lobe, precentral gyrus, Brodmann area 6
	−22	4	58	−22	7	53	left frontal lobe, sub-gyral, Brodmann area 6

[1] *MNI* Montreal Neurological Institute.
[2] Derived by Talairach daemon client 1.1 software (The Research Imaging Center, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA).

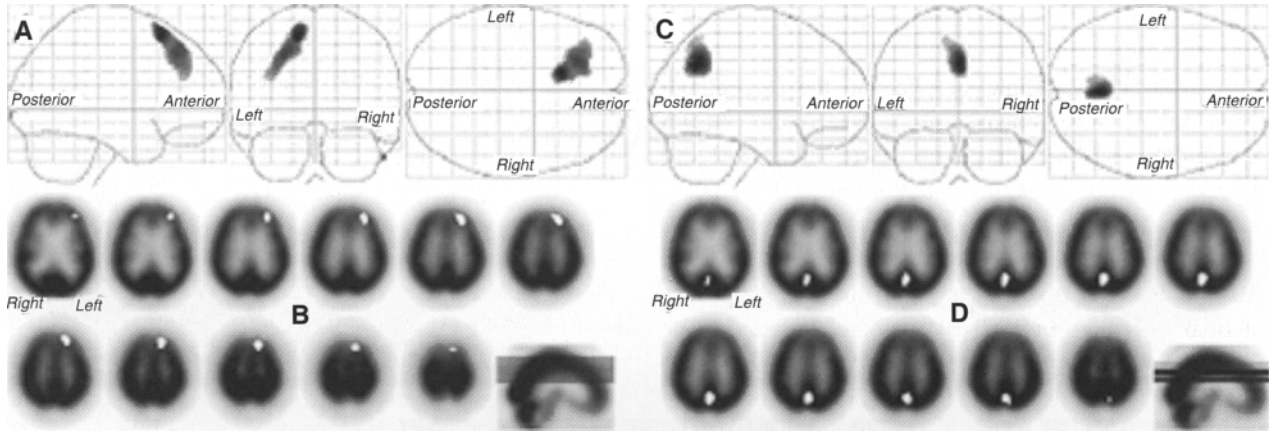

Fig. 3. A significant regional cerebral perfusion difference occurred between the good and poor responder groups

comparison and at cluster-level $p<0.001$ corrected for multiple comparison. Figure 1 shows these clusters had significantly increased rCBF after MNS in the maximum projection images (glass brain) of the transaxial, coronal and sagittal views. Figure 2 shows these clusters overlaid on the mean image of the spatially normalized and smoothed SPECT images of all patients. Table 2 shows the size (in voxels) and *P* value of these clusters, the Montreal Neurological Institute (MNI) coordinates (in *x*, *y* and *z*), and *P* value of local maxima more than 8.0 mm apart in each cluster. Table 3 shows the anatomical location of local maxima in each cluster as MNI coordinates, Talairach and Tournoux coordinates (in *x*, *y*, and *z*), and the corresponding anatomical regions. There is no significant regional decrease of cerebral perfusion after MNS in the GR group.

In the PR group, paired Student *t*-test did not show any significant increase or decrease of rCBF after MNS.

When assessing the significant differences between the GR and PR groups, two-sided two-sample Student *t* test revealed a cluster of between-group differences (the rCBF of the GR was higher than the PR group) in the left frontal lobe (with a 698 voxel size with cluster level $P=0.017$ corrected for multiple comparison) as shown in Fig. 3 A and B. Two-sided two-sample Student *t* test of the rCBF in the PR group that was higher than in the GR group showed a cluster in the occipital, parietal lobes, and posterior cingulated gyrus (554 voxel size with a cluster level $P=0.032$ corrected for multiple comparison) as shown in Fig. 3C and D. These clusters of between-group differences shared no mutual voxels with the clusters with significant regional effects after MNS.

Discussion

In the present study, we examined the effect of electrical right MNS on rCBF in brain-damaged patients. The main findings are that, in brain damaged patients following 4 weeks of stimulation of the right median nerve, the GR group showed a significant increase in rCBF in the regions of the precentral gyrus, midfrontal gyrus, superior frontal gyrus, subgyral, inferior parietal lobule, and postcentral gyrus corresponding to Brodmann areas 4, 6, and 40. Conversely, the PR group did not show a significant increase of rCBF in the brain. Electrical MNS is used to investigate mainly the hand area of the somato-

sensory cortex in neurophysiological studies using somatosensory evoked potential (SEP), positron emission tomography (PET), evoked magnetoencephalography (MEG) signals, and functional magnetic resonance imaging (fMRI) [15–20]. Our results in the GR group (but not in the PR group) are in line with previous reports of stimulation of the primary somatosensory cortex (Brodmann area 3) [21–24].

Zifko *et al.* performed ^{99m}Tc-ECD SPECT during electrical MNS to detect focal neuronal activation in the somatosensory pathways [25]. They found regions of difference between baseline and activation in the postcentral gyrus (17%), posterior parietal lobe (14%), precentral gyrus (12%), and cerebellar hemisphere (8%). Our results do not show an effect in the cerebellum. Decreased perfusion changes in the cerebellum (8% vs. 17%, 14%, and 12%) may account for the lack of significant perfusion increases noted in our study.

Our results in the GR group (but not in PR group) also show increased rCBF in the inferior parietal lobule (Brodmann Area 40), which is compatible with the results of Boakye *et al.* using fMRI [26]. A recent study using fMRI to assess contralateral and ipsilateral responses in primary somatosensory cortex following electrical MNS in 10 healthy volunteers found that both the contralateral primary somatosensory cortex and the ipsilateral primary somatosensory cortex were activated following median nerve stimulation [17]. Some researchers have also reported the activation of the ipsilateral cortex [27, 28]. Our results do not show any ipsilateral activation clusters. The small sample size in our study and the differences in our subjects (brain damaged patients versus healthy volunteers) may account for some of the reasons for this lack of activation in this particular area.

Our results demonstrate the early effect (4 weeks) of MNS on rCBF. Due to the retrospective nature and small sample size of our study, further investigation of the prognostic value of this activation phenomenon is necessary to clarify whether this early effect may be useful in predicting the effectiveness of prolonged (longer than 4 weeks) MNS therapy.

Conclusion

Our results show that MNS enhances rCBF of the contralateral motor and somatosensory cortex. These findings are compatible with the few previous functional studies. Further research is necessary to determine whether the enhanced rCBF may help to predict the effectiveness of prolonged MNS.

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Acta Neurochir Suppl (2008) 101: 71–76

Printed in Austria

Effects of electrical cervical spinal cord stimulation on cerebral blood perfusion, cerebrospinal fluid catecholamine levels, and oxidative stress in comatose patients

J.-T. Liu, W.-C. Tan, W.-J. Liao

Department of Neurosurgery, Chung Shan Medical University Hospital, Taichung, Taiwan

Summary

Objectives. Electrical spinal cord stimulation (SCS) is used to treat of chronic pain, obstructive arterial-related ischemia, and anginal pain. This study investigated cerebral blood perfusion, cerebrospinal fluid (CSF) catecholamine levels, and oxidative stress before and after cervical SCS in comatose patients.

Methods. We evaluated cerebral blood perfusion, catecholamine (dopamine, norepinephrine, and epinephrine) levels, and oxidative stress in 20 comatose patients before and after SCS. After SCS for six months, cerebral blood perfusion (SPECT index, 2.293 ± 0.255 *vs.* 2.779 ± 0.209, $p < 0.001$), dopamine (49.0 ± 12.1 *vs.* 198.9 ± 62.6, $p = 0.025$), and norepinephrine (197.6 ± 62.9 *vs.* 379.6 ± 52.6, $p = 0.021$) but not epinephrine were significantly increased. Moreover, superoxide free radicals in whole blood were significantly decreased ($210{,}079 \pm 47{,}763$ *vs.* $109{,}212 \pm 20{,}086$, $p = 0.011$) after SCS. Nine patients recovered from the consciousness within 71–287 days.

Conclusions. Increase of cerebral blood perfusion and catecholamines (dopamine and norepinephrine) in CSF after SCS was observed, whereas epinephrine level was unchanged. The superoxide free radicals were decreased after SCS. The results suggest that SCS increases cerebral blood perfusion, attenuates oxidative stress and increases biogenic amines in comatose patients.

Keywords: Catecholamines; cerebral blood perfusion; comatose patients; electrical spinal cord stimulation; oxidative stress.

Introduction

Advances in care of acute brain injury have significantly improved the survival of traumatic or non-traumatic (often anoxic) patients. However, because a substantial proportion of survivors develop a vegetative state, severe brain injury remains a major cause of morbidity [2]. Data from one traumatic coma databank showed that 14% of patients with severe closed-head injury were discharged in a vegetative state [12]. A multi-society task force defined persistent vegetative state (PVS) as the presence of a vegetative state one month or longer after acute traumatic or non-traumatic injury [1].

Electrical spinal cord stimulation (SCS), which has a validated use for the treatment of angina pectoris [4] was used successfully for the treatment of ischemic diseases, including vasospastic and peripheral vascular disease [18]. It is believed that functional reversible sympathectomy may be a possible mechanism for SCS [14]. SCS also improved both cerebral blood perfusion and motor performance of stroke patients [20]. The commonly used semi-quantitative technique to measure cerebral blood perfusion is transcranial Doppler (TCD) or single photon emission computed tomography (SPECT) [21].

The SCS phenomenon relieving pain in neurogenic disease [3] is associated with the release of neurotransmitters involved in pain control [5]. It has been shown that catecholamine (epinephrine, norepinephrine, and dopamine) serum levels in patients with brain injury appeared to fall after brain death [17]. On the other hand, oxidative stress is believed to strongly influence the neurological recovery of patients following a severe head injury. Estimation of the markers of oxidative stress in the blood of such patients can hence aid in predicting the prognosis of head injury [2]. Thus, the aim of the present work was to investigate the SCS induced effect on vasodilator, release of catecholamines in CSF, and oxidative stress modification in comatose patients.

Patients and methods

Patient population

Twenty patients (13 men, 7 women) in a vegetative state who had received median nerve stimulation for three months in 19 cases and

Correspondence: Dr. Wen-Jui Liao, Department of Neurosurgery, Chung Shan Medical University Hospital, No. 110, Sec. 1, Chien-Kuo N. Road, Taichung 402, Taiwan. e-mail: cshy660@csh.org.tw

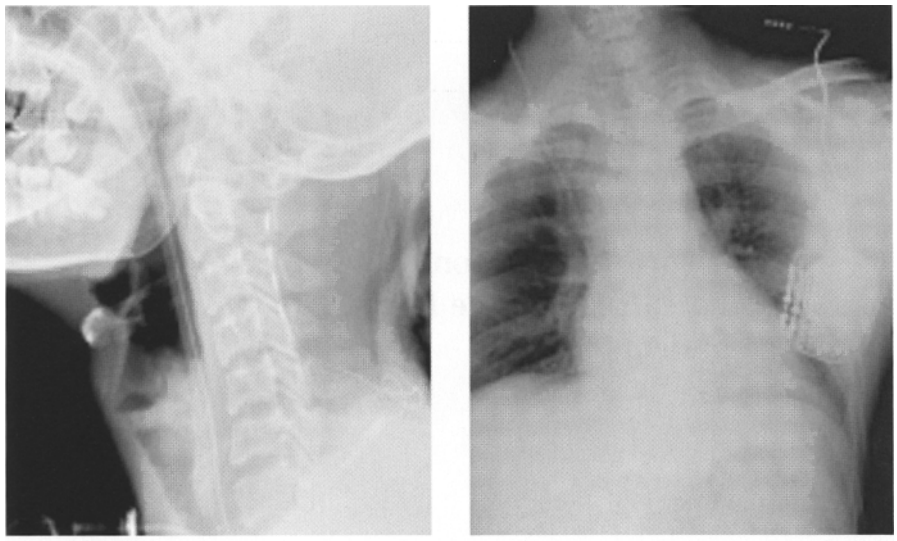

Fig. 1. Spinal stimulation for the treatment of a vegetative state patient. The stimulating electrode was placed on the posterior surface of the spinal cord at C2-4, in the epidural space (A). A subcutaneous impulse generator provided an adjustable range of pulse width, intensity, and frequency of stimulation (B)

14 days in one case without improvement in consciousness were enrolled and began treatment with cervical SCS at Chung-Shan Medical University Hospital, Taichung, Taiwan between February 2004 and February 2006. Inclusion criteria were absence of fever and stable vital signs. Exclusion criteria included a toxin- or chemical-induced coma, hepatorenal failure, cervical cord injury, central nervous system infection, local infection of an operative area, or inappropriate candidate for general anesthesia. Written consent was obtained from each respective guardian or legal next of kin. SPECT imaging, Glasgow Coma Scale (GCS) and Persistent Vegetative State (PVS) Scores, as well as necessary feeding and respiratory assistance, were recorded before, during, and after the treatment with SCS.

Spinal cord stimulation

Neurostimulation was performed using a Medtronic system (Medtronic Neurological, Minneapolis, MN). A four-contact resume electrode (3587A, Medtronic Inc., Minneapolis, MN, USA) was inserted with a small laminectomy at lower edge of C4 following administration of a general anesthesia [6]. An electrode was placed on the posterior surface of the spinal cord at C2-4, in the epidural space (Fig. 1A). A subcutaneous impulse generator provided an adjustable range of pulse width, intensity, and frequency of stimulation (Fig. 1B). The parameters of the stimulator were set at 1.0–4.7 V, a pulse width set between 120 and 210 μsec, and a rate of 60–100 Hz. The stimulation regimen was set as 15 min on/15 min off for duration of 10 h during the daytime.

Single-photon emission computed tomography

The blood flow measurements during SPECT scanning were obtained 10 min after intravenous administration of 740 MBq of ^{99m}Tc-HMPAO, which is capable of crossing the blood-brain barrier and its intracranial distribution is proportional to blood flow [6]. Semiquantitative indices were obtained in these areas by using the cerebellum as a reference.

Measurement of superoxide free radicals in whole blood

Immediately after the blood was drained, 3.9 ml lucigenin were added to 600-μm whole blood samples (as a concentration of 2 mM) in a plastic tube cuvette. The photon emissions at 200–750 nm were then measured using the BJL-Ultra-Weak Chemiluminescence Analyzer (American Biologics, sensitivity 1.85×10^{-17} W/cm^2 · count) for 60 min. The total and peak counts of superoxide free radicals were recorded and suggested as an index for intravascular oxidative stress [13].

Catecholamine assay

High performance liquid chromatography was used for catecholamine analysis, 5 ml CSF was collected. After centrifugation, CSF was frozen and stored at −20 °C till analysis. CSF was analyzed for epinephrine, norepinephrine, and dopamine employing HPLC (D7000, Merck Germany) with electrochemical detector [10].

Statistical analysis

Data are expressed as mean ± SEM. Differences in quantitative outcome measures between baseline and half year for each patient were assessed with the paired Student's *t*-test test; significance was defined as $p < 0.05$.

Results

Clinical assessment

Baseline age, duration of coma, and GCS scores are shown in Table 1. The 20 patients were relatively young (mean age, 30 years; range, 19–47) and had a mean coma duration of 623.75 ± 160.07 days (range, 132–2875). Etiologies of injury were contusional intracranial or subarachnoid hemorrhage due to trauma (twelve patients), carbon monoxide intoxication (three patients), electric shock (one patient), drug allergic shock (one patient), Cardiogenic shock (two patients) and rupture of an arteriovenous malformation (one patient). Over the course of treatment, nine patients emerged from coma (patient can follow a simple order); this transition occurred on days 64, 66, 70, 85, 107, 140, 185 and 156 for patients 1–4, 6, 7, 10, 14, and 17, respectively.

Table 1. *Patients' characteristics*

No.	Age	Sex	Injury category	Surgery	CT and SPECT scan	Comatose period
1	21	M	SAH, subdural hematoma, pulmonary embolism	V-P shunting tracheostomy	brain atrophy 0.83/1.91	207 days GCS 8–15 waking time: 64 days
2	21	F	SAH, subdural hematoma,	craniectomy, cranioplasty, V-P shunting tracheostomy	brain atrophy 0.85/1.48	330 days GCS 9–15 waking time: 185 days MC: 66 days
3	22	M	SAH, subdural hematoma,	craniectomy, cranioplasty V-P shunting, tracheostomy	brain atrophy 2.15/2.57	364 days GCS 9–15 waking time: 107 days
4	42	F	SAH, subdural hematoma,	V-P shunting tracheostomy	brain atrophy 2.58/2.53	265 days GCS 8–15 waking time: 140 days MC: 64 days
5	26	M	subdural hematoma, intracerebral hematoma (pontine hemorrhage)	V-P shunting tracheostomy	tissue loss on pons 4.13/4.68	251 days GCS 9–9
6	26	F	CO intoxication	tracheostomy	brain atrophy 2.9/3.9	132 days GCS 9–15 waking time: 85 days MC: 30 days
7	19	M	SAH, subdural hematoma,	craniectomy, cranioplasty V-P shunting, tracheostomy	brain atrophy 1.79/2.06	280 days GCS 10–15 waking time: 107 days
8	27	M	SAH, subdural hematoma, ICH	craniectomy, cranioplasty V-P shunting, tracheostomy	brain atrophy 0.5/1.95	218 days GCS 8–8
9	47	M	cardiac arrest, hypoxia	nil	normal brain 4.6/4.82	156 days GCS 10–10
10	28	M	SAH, subdural hematoma, Diffuse axon injury	V-P shunting tracheostomy	brain atrophy 2.68/3.1	181 days GCS 9–15 waking time: 70 days
11	39	F	AVM, right side intracerebral hematoma	craniotomy V-P shunting tracheostomy	brain atrophy 0.75/2.04	2875 days GCS 7–9 MC 133 days
12	27	M	SAH, subdural hematoma, diffuse axon injury, ICH	craniotomy V-P shunting tracheostomy	brain atrophy 2.75/2.90	218 days GCS 8–10
13	26	M	SAH, subdural hematoma, ICH	caniotomy V-P shunting tracheostomy	brain atrophy 2.7/3.16	1207 days GCS 8–10
14	35	M	CO intoxication, cardiac arrest	V-P shunting tracheostomy	brain atrophy 2.63/3.32	2017 days GCS 10–15 waking time: 166 days
15	31	F	drug allergy, cardiac arrest	tracheostomy	brain atrophy 2.15/2.98	433 days GCS 7–10 MC 154 days
16	34	M	cardiogenic shock	tracheostomy	brain atrophy 2.57/2.80	1179 days GCS 7–9
17	45	F	SAH, subdural hematoma, ICH	craniotomy V-P shunting tracheostomy	brain atrophy 1.73/1.9	241 days GCS 9–15 waking time: 85 days MC: 60 days
18	26	M	SAH, subdural hematoma, ICH (Pontine hemorhage)	craniotomy V-P shunting tracheostomy	brain atrophy tissue loss on pons 3.9/3.2	359 days GCS 7–9
19	27	M	CO intoxication, cardiac arrest	V-P shunting tracheostomy	brain atrophy 0.98/1.47	977 days GCS 8–9
20	31	F	drug allergy, cardiac arrest	V-P shunting tracheostomy	brain atrophy 2.69/2.82	585 days GCS 7–9 MC 192 days

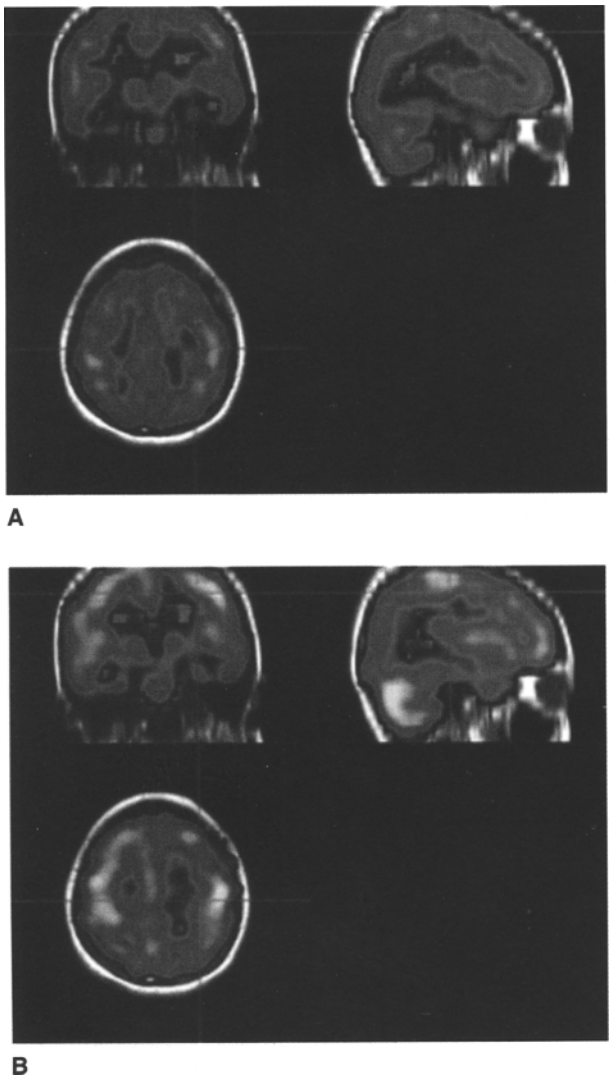

Fig. 2. The cerebral perfusion increased after stimulation

The mean age and coma duration of these nine patients were 26 years (range, 21–42) and 238 days (range, 132–364) compared with the values for the group as a whole of 29 years and 459 days.

SPECT index

Figure 2A and B shows the dramatic increase of cerebral perfusion after stimulation. SPECT results revealed that cerebral perfusion was significantly increased post-treatment (SPECT index, 2.293 ± 0.255 *vs.* 2.779 ± 0.209, $p < 0.001$, 21.2% increase) (Fig. 3A). Similarly, the GCS and PVS state and reaction scores improved significantly from baseline to post-treatment (all three $p < 0.05$). No surgical complication was found in any patient, and no clinical deterioration has been noted at a median follow-up of 23 months (range, 18–30 months).

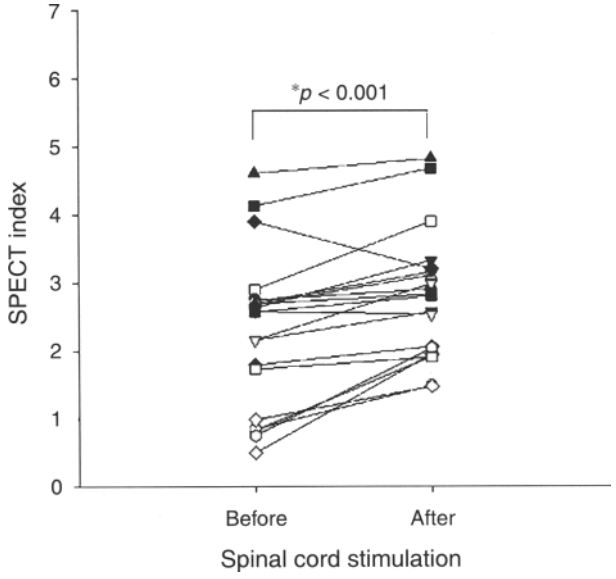

Fig. 3. SPECT index before and after stimulation ($n = 20$, $^*p < 0.05$)

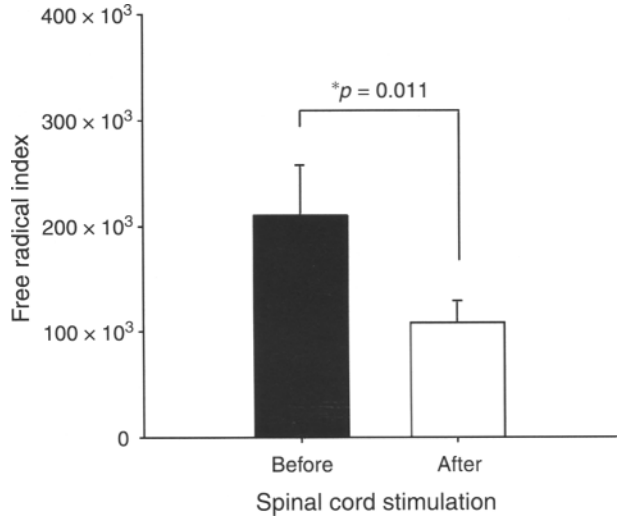

Fig. 4. Free radical index before and after stimulation. Data are expressed as mean ± SEM ($n = 20$, $^*p < 0.05$)

Free radical index

As shown in Fig. 4 patients after SCS had significantly lower total counts of superoxide free radicals in the whole blood ($210{,}079 \pm 47{,}763$ *vs.* $109{,}212 \pm 20{,}086$, $p = 0.011$, 48.0% reduction).

Catecholamine levels

Catecholamine (epinephrine, norepinephrine, and dopamine) levels in CSF were measured by HPLC. As shown in Table 2, dopamine (49.0 ± 12.1 *vs.* 198.9 ± 62.6, $p = 0.025$, 305.9% increase), and norepinephrine

Table 2. *Levels of catecholamine (dopamine, norepinephrine, and epinephrine) in cerebrospinal fluid before and after spinal cord stimulation*

Catecholamine	Before	After	p value
Dopamine (pg/ml)	49.0 ± 12.1	198.9 ± 62.6	0.03*
Norepinephrine (pg/ml)	197.6 ± 62.9	379.6 ± 52.6	0.02*
Epinephrine (pg/ml)	<10	<10	NS

* Significant $= p < 0.05$.
NS no statistical significance.

(197.6 ± 62.9 *vs.* 379.6 ± 52.6, $p = 0.021$, 92.1% increase) but not epinephrine were significantly increased after SCS.

Discussion

In the present study, we described the effects of the SCS on the increase of cerebral blood perfusion, and investigated the changes of oxidative stress and catecholamine levels in CSF. The results showed that (i) cerebral blood perfusion was enhanced after SCS, (ii) catecholamine (dopamine and norepinephrine) levels in CSF were increased after SCS, although epinephrine level was unchanged, (iii) the superoxide free radicals in whole blood were decreased after SCS. These data suggests that SCS could attenuate oxidative stress and increase biogenic amines followed by an increase of cerebral blood perfusion in comatose patients.

SCS is a viable option for treatment of angina pectoris and inoperable peripheral vascular diseases (PVD) [9]. The mechanism of action remains controversial, but successful pain relief has been consistently reported [9]. SCS is a reversible procedure, with the stimulation devices implanted subcutaneously; neurostimulation can proceed over protracted periods of months or even years. The stimulation devices can be also switched on and off at any time and can be activated as required within the patient's other therapy schedules. In addition, clinical studies showed that SCS induced cerebral blood perfusion augmentation has led some clinicians to use this procedure in the treatment of cerebral ischemia [8, 19] and persistent vegetative states [22]. Nevertheless, despite the promise of clinical benefit from SCS in the treatment of cerebral ischemia, its effective use has been hampered by a lack of understanding of its mechanism(s) of action.

In the study, we evaluated whether the clinical blood flow improvement after SCS in comatose patients is associated with changes in CSF levels of catecholamines involved in pain modulation or vascular resistance control. Our results showed that after a period of SCS, comatose patients exhibited an improvement of cerebral blood perfusion and neurotransmitter pattern characterized by higher levels of norepinephrine and dopamine were observed. Previous study reported that dorsal column stimulation (DSC) improves the clinical symptoms of cases in PVS. The biochemical changes in CSF caused by DCS in patients in PVS; neurostimulation enhanced the metabolism of catecholamines in CSF, norepinephrine, dopamine, and 3,4-dihydroxyphenylacetic acid, increased, but 3-methoxytyramine and 5-hydroxytryptamine decreased in CSF. DCS increased cerebral blood perfusion, enhanced the metabolism of catecholamines in CSF, and improved the EEG in patients in PVS [7]. These data suggests that the CSF catecholamines response to SCS could have clinical value in predicting the success of treatment.

Recently, poor neurologic outcome was found to associate with increased levels of oxidative damage [7]. Another study also suggests that a condition of oxidative stress occurs in patients with head trauma and hemorrhagic stroke of recent onset [16]. Although oxidative stress may be important in the development and progression of brain injury, most of the oxidative stress markers currently used in clinical evaluation are rather indirect. In the present study, basal superoxide generation in whole blood was measured immediately after blood sampling. This measurement could directly reflect, at least in significant part, the immediate status of intravascular oxidative stress in comatose patients. Our results showed that superoxide free radicals in whole blood was significantly decreased after SCS suggesting the potential benefit of SCS on oxidative stress modulation. However, the underlying mechanisms remain to be addressed in further studies.

There are some limitations of this study. For example, over the course of treatment, nine patients emerged from coma, however, under the same circumstance; the other 11 patients were still in comatose state. In addition, our patient sample size was small; the data might be of limited value and therefore an additional study of more cases is needed.

In conclusion, our data suggests that SCS exerts its beneficial effects by increasing the cerebral blood perfusion and catecholamines (dopamine and norepinephrine) in CSF; and SCS attenuated the superoxide free radicals in whole blood. Nevertheless, more research needs to be done to confirm the positive effects of SCS in observational study. A better understanding of the mechanism(s) involved in the SCS-induced effect on cerebral blood perfusion is crucial and will allow more effective clinical use of this procedure in the treatment of cerebral ischemia.

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Acta Neurochir Suppl (2008) 101: 79–81

Printed in Austria

Strategic plan: building a international strategy for risk reduction supercourse

R. E. LaPorte[1], W.-T. Chiu[2]

[1] WHO Collaborating Centre, Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA, USA
[2] Department of Neurosurgery, Taipei Medical University-Wan Fang Hospital; Graduate Institute of Injury Prevention and Control, Taipei Medical University, Taipei, Taiwan

Summary

There is an important need to develop a global expert disaster network for Mitigating against disasters such the Chi-Chi Earthquake, the Tsunami, Avian flu. This systems needs to target both man made and natural disasters. We propose the building of a Global Health Disaster Network, with advanced features such as educational capabilities, and expert knowledge reachback. We provide a strategic plan to building a global disaster Network and Mitigation system.

Keywords: Disaster mitigation; internet.

In 1995, we published in the BMJ that there was a critical need for a Global Health Disaster Network (http://www.bmj.com/cgi/content/full/310/6991/1412/a). At that time both natural disasters e.g. Kobe, and man-made, Chechnya, Bosnia, Rwanda, had just occurred.

Considerable progress has been made, such that with more recent disasters such as the Chi-Chi, and Bam Earthquake experts need to be rapidly mobilized, trained and coordinated. Neurosurgeons need to work with Structural engineers, psychologists, nurses, public health and first responders to reduce the loss of life and minimize long term sequela. Coordination and education across our silos of disciplines is essential, but very difficult as we have different cultures. Local, National and International agencies such as WHO or the UN have not found as yet an effective system to allow this to occur. Here we describe a new approach, the Global Health Network and the Supercourse.

Correspondence: Ronald E. LaPorte, WHO Collaborating Centre, Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA 15261, USA. e-mail: ronaldlaporte@gmail.com

The Global Health Network and the Supercourse has been built upon a simple set of principles (www.pitt.edu/~super1). The first is that the Internet and other IT are ideally suited for networking. Secondly it is better to have a network of Neurosurgeons, Public Health experts, and engineers on the ground before an earthquake, rather than try to build it immediately afterwards.

During the early 1900s a group of us started to construct a global health network. The idea was simple. Taiwan and the world has seen a 30 year increase in life expectancy since 1950. It has been estimated that 25% of the increase was due to public health measures such as nutrition and helmet laws. Most of prevention is the sharing of information, therefore if we could harness the information technology revolution we could have a profound effect on health.

In the past few years the Internet has been recognized not only as a tool that can share billions of bites of information almost immediately. It has also be recognized that the Internet is a social phenomena, where friendship can easily be formed and we can cut across disciplines to communicate with each other to a degree never before possible.

We have built on the power of the Internet to form social communities to build the Global Health Network (GHNet). The GHNet evolved from meetings that the World Health Organization and the Pan American Health Organization. The idea was to network all academic scientists interested in prevention. If there was an earthquake in Pittsburgh, we could tap into the expertise of neurosurgeons who helped with the Chi-Chi earthquake. If a case of west Nile Fever occurred in Mexico City, scientists could tap into experts in Cairo.

The GHNet demonstrated immediate success, as in a period of 5 years it grew from less than one hundred people to now greater than 45,000 in 174 countries, a remarkable growth. These included global health experts, but also neurosurgeons, many different specialties in medicine and other scientific disciplines. As we developed the network we saw some of the power of the Internet approach could be in education. In the British Medical Journal we proposed that a Global Health Network University could be built (http://bmj.com/cgi/content/full/309/6956/736).

In the past few years the Global Health Network has taken on a new mission, that of the improvement of prevention and disaster education. Here to the concept is simple. Dr. Chiu is an expert in the prevention of head injuries, Dr. LaPorte is not. If Dr. LaPorte had Dr. Chiu's lecture on head injuries he could teach this in his students. Similarly, Dr. LaPorte is an expert on Type 1 diabetes. Type 1 diabetics have a 6 fold increase in traffic accidents, thus if Dr. Chiu wanted to present on diabetes and crashes, he could use the materials from Dr. LaPorte.

The backbone of this effort is "PowerPoint" on the web. PowerPoint and the Internet may be the most important educational technology in the past 2 centuries. Before PowerPoint on the web when we would teach on the chalk board, at the end of the class we would wipe the board, clap the erasers, and the lecture would be gone forever. Now when we end the class, the lectures are put onto the web, saving the knowledge for decades.

The Supercourse leverages the power of PowerPoint by creating an open source lecture library that anyone can use for free from any different discipline. We were the first people to build a PowerPoint lecture library and the response was extraordinary. Over a period of 7 years we have collected 3328 lectures across a wide spectrum of areas.

GHNet, supercourse and disasters

A primary target area of ours has been the application of the GHNet, and Supercourse to disaster mitigation. There are several major components for this.

1. Expert Knowledge Reachback: One of the major difficulties of a disaster is rapidly finding the expertise needed and available. For example should there be a large number of people with crush injuries and kidney failure, how does one rapidly obtain the expertise to treat these. We have a network of 45,000 people world wide who are interested in prevention. However, our available network is much larger than this as scientists know scientists. Thus neurosurgeons know engineers, psychologists know business people. The concept of expert Knowledge Reachback is that none of us know everything needed about say the Chi-Chi earthquake. However, by probing the network we can fing the expertise needed. Alternatively the network is within one degree of separation of the expertise that is needed.

2. Expert Lectures: On the Supercourse we have 270 different lectures about disasters (http://www.pitt.edu/~super1/assist/topicsearch.htm). Each one of these can easily be modified for local circumstances. For example we have 4–5 lectures on disposing of dead bodies. Within about a hour the lectures could have been customized to the Chi-Chi or Bam earthquake, providing easily understandable educational materials. The lectures could also be customized to medical workers in the hospitals or first responders. This is one of the largest collections of educational materials.

3. Just in Time lectures: A major problem of education in disasters is that it comes too late and the materials are of questionable scientific value. A few years ago on Dec. 28 the Tsunami swept across Asia. Few people knew what a tsunami was. We sent a note out to our network of 45,000 and they immediately responded. They did not have all the expertise to help, but they knew oceanographers, meteorologists, disaster experts, etc. An expert in disasters in Tehran, a cardiologist from Novosibirsk Russia, and an epidemiologist from Pittsburgh gathered the expert knowledge and constructed in 2 days a lecture on "what is a Tsunami" (http://www.pitt.edu/~super1/lecture/lec18091/original.ppt). Within a week the lecture was released world wide, and translated into many different languages. We were able to teach over 200,000 people in 120 countries. To our knowledge, this is one of the largest number of students taught with a single lecture.

Our Just-in-Time lecture has proven to be very successful. We target not only people at ground zero, but also all others in that country. To illustrate, we were in Pakistan at the time of the Pakistani earthquake. In Pakistan we have a network of over 600 people available. When the Pakistani earthquake struck, it particularly affected the schools with floors "pan caking" on top of each other causing severe head injuries and death. Immediately afterwards about the only

thing seen of TV was dead children being pulled from the hospitals. The earthquake was devastating, but perhaps what may have been even more harmful in the long run was that many students in the rest of the country stopped going to school. We created a JIT lecture for Taiwan, using core materials from the Bam Earthquake, and distributed this to over 10% of the schools (http://www.pitt.edu/~super1/lecture/lec21271/index.htm).

The importance of our network also was demonstrated as we were able to refer 40 trained public health workers to the World Health Organization who network in Pakistan was substantially smaller than ours.

Conclusions

The Power of the Global Health Network and the Supercourse is in the diverse interdisciplinary network. We very much want to bring more neurosurgeons into the network who are interested in disasters and prevention and general.

Future

We are under discussions with the World Health Organization and the United Nations about building a WHO Supercourse for disasters. This would become the umbrella for educational materials and the cornerstone for disaster education for the future.

Acta Neurochir Suppl (2008) 101: 83–86

Printed in Austria

Endovascular procedures for cerebrovenous disorders

F. Y. Tsai[1], B. Nguyen[1], W.-C. Lin[2], C.-J. Hsueh[3], A. Yen[1], K. Meng[1], V. Kostanian[1]

[1] UC Irvine Medical Center, Orange, CA, USA
[2] Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
[3] Triservices General Hospital, Taipei, Taiwan

Summary

Cerebral venous anomalies may have a variety of clinical consequences. MR or CT venogram can assist the imaging diagnosis; yet, cerebral angiogram may be required to confirm or establish the correct diagnosis. Venous anomalies predisposing venous hypertension may be categorized into three major entities such as congenital variations, outflow obstruction, and increased blood flow. The degree of clinical presentations of venous hypertension depends upon the chronicity or acuteness. Venous hypertension may lead to venous congestion with edema, hemorrhage and encephalopathy. Endovascular therapeutic procedures may be employed to relieve venous congestion either from reducing blood flow or relieving obstruction. Those endovascular treatment options include embolization, thrombolysis and angioplastic stentings.

Keywords: Cerebral; venous; hypertension; embolization; thrombolysis; stent.

Introduction

The cerebral venous system may be so varied as to be considered normal. However, what is frequently called normal may in actuality represent an abnormal pathological disorder. The purpose of this investigation is to review our experiences with various cerebral venous disorders in hopes of providing a means to avoid potential mismanagement.

Materials and methods

We have retrospectively reviewed 1500 cerebral angiograms at our institution over the past 5 years and separated cases of venous anomalies into one of three major entities: [1] congenital variations (hypoplasia, atresia, or ectasia); [2] outflow obstruction (atresia, stenosis, or thrombosis); and, [3] increased blood flow (AV malformation or fistula). Additionally, we went further by analyzing a subgroup of patients with cerebral arterial aneurysms treated at our institution from March 2004 to July 2007. Two hundred fifty patients were identified, of which 88 were excluded due to an incomplete angiogram or inadequate venous phase. We reviewed the dural sinus patterns and applied the Chi-squared goodness-of-fit statistic with a 0.05 level of significance to determine any association with aneurysmal rupture. A CTA or MRA often preceded the invasive diagnostic and/or therapeutic cerebral angiograms. Therapeutic procedures were performed using a 6F guiding catheter or long sheath in adults.

In pediatric patients, we used 4F or 5F sheaths. Two kinds of coils were used in this series: GDC and Cerecyte. Liquid embolic agents were glue and onyx. Stents and balloon catheters depended on the diameter and length of the vessel in question for treatment.

Results

Of the 1500 cerebral angiograms reviewed, more than 68% demonstrated asymmetry and/or hypoplasia of the dural sinus. In our series, hypoplastic dural sinuses almost always involved the transverse and sigmoid sinuses. About 3% involved the frontal superior sagittal sinus.

We reported experience with the following: 32 patients with acute dural sinus thromboses (ages 19–77 with average 32.9 years, female:male ratio 19:13); 7 patients with venous angiomas (ages 36–72 with average 49 years, female:male ratio 4:3); 13 with dural sinus stenosis (ages 14–72 with average 45.6 years, female:male ratio 11:2); 8 patients with atresia of dural sinus (ages 36–72 with average 57.6 years, female:male ratio 6:2); 13 patients with dural sinus fistulas (ages 40–71 with average 65.2 years, female:male ratio 7:6); and, 4 patients with a giant venous aneurysm with AVM (newborn, 3–50 years with average 12.5 years, female:male ratio 3:1)

Of the 162 patients with cerebral aneurysms (age 15–90 with average 54.6 years, female:male ratio 104:58), 110 patients had ruptured aneurysm and 52 patients had incidental cerebral aneurysm. Among those 52 patients without ruptured aneurysm, there were 34 females and

Correspondence: Fong Y. Tsai, MD, Department of Radiological Sciences, UC Irvine Medical Center, 101 City Drive South, Orange, CA 92868, USA. e-mail: ftsai@uci.edu

18 males. Thirty-one patients had asymmetry and 21 patients had symmetry of dural sinus. However, a significant association was demonstrated between ruptured aneurysms and asymmetry of the dural sinuses. Namely, among those 110 (female:male ratio 70:40) patients who had ruptured aneurysms, 85 of these 110 patients had asymmetry while only 25 patients had symmetry of dural sinus. It was even more significant in those 70 female group; 55 of 70 females demonstrated asymmetry and 25 had symmetry of dural sinus. Of the 40 males, 30 had asymmetry and 10 had symmetry of dural sinus.

Illustrative cases

Case 1 (Fig. 1). A 76 year old female presented massive grade 4 subarachnoid hemorrhage (SAH) after a severe headache. Head CT showed massive subarachnoid and ventricular hemorrhage. Cerebral angiogram discovered an acute ruptured right posterior communicating aneurysm with severe hypoplasia of right transverse and sigmoid sinuses. Prominent right cortical (Trolard) vein was noted as collaterals for right cerebral venous drainages (as seen in Fig. 1d). Aneurysm was then successfully coiled.

Case 2 (Fig. 2). A 52 year old male presented with long standing headaches and left trigeminal neuralgia. Head CT and MRI demonstrated ventricular enlargement. Contrast MRI showed possible stenosis at the junction of the left jugular vein and sigmoid sinus. He presented more severe headache and altered mentation after an operation of trigeminal neuralgia. Increased density was noted at the left transverse sinus on CT after surgery and corresponded to nonvisualization of left transverse sinus on MR venogram. Cerebral angiogram confirmed thrombosis as well as stenosis. Cerebral circulation was delayed, taking more than 14 sec to see venous system during carotid angiography. Balloon assisted thrombectomy and thrombolysis with 4 mg of tPA

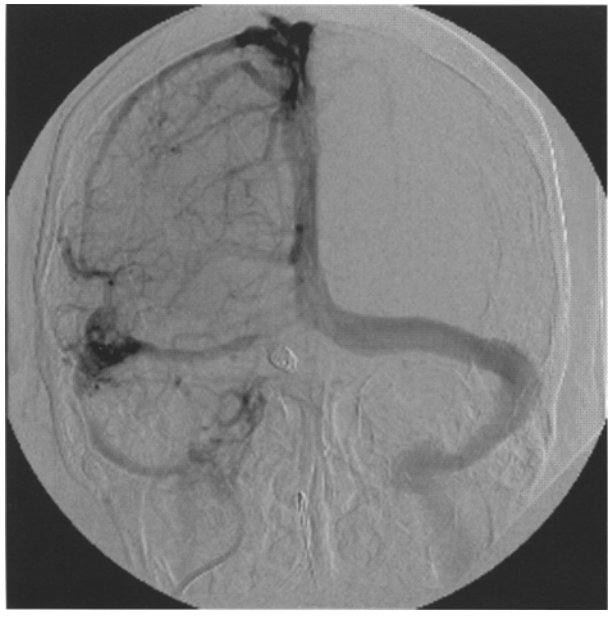

Fig. 1. Frontal view of post coiling angiogram showed successful coil occlusion of aneurysm and hypoplasia of righ transverse and sigmoid sinuses

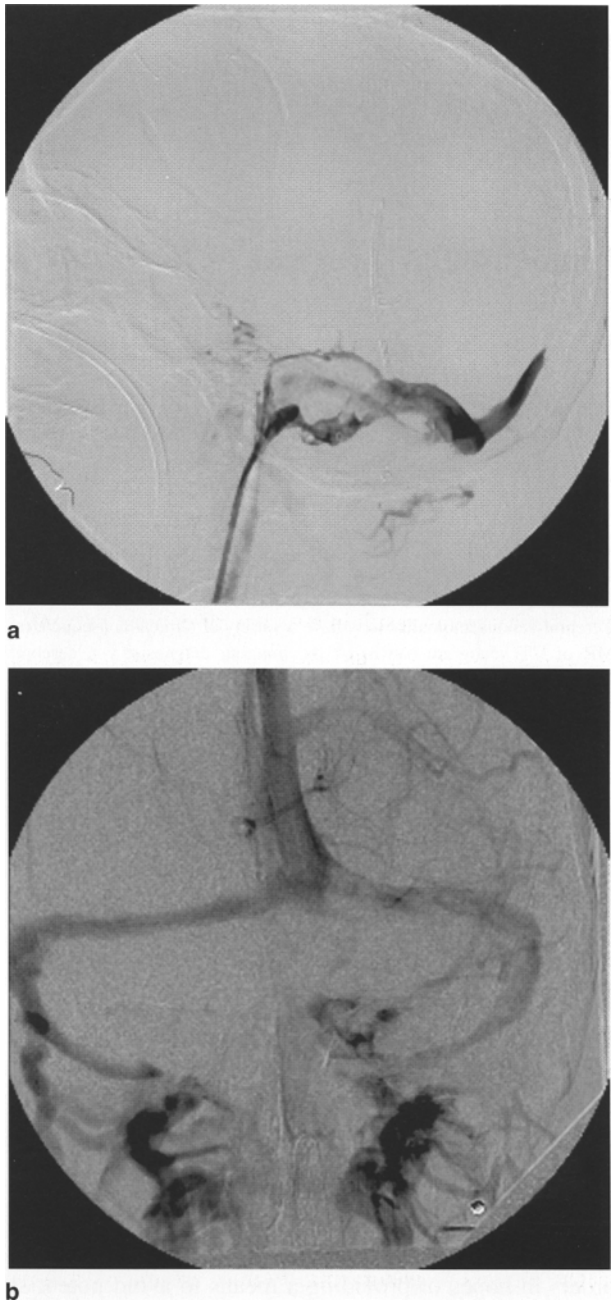

Fig. 2. (a) Cerebral venogram showed severe stenosis of distal left simoid sinus with partial rethrombosis. (b) Repeat angiogram showed recanalization of entire left dural sinuses after angioplasty and balloon assisted thrombectomy and thrombolysis

and angioplasty of the stenosis with 8 mm balloon were performed with good recovery.

Discussion

Recent advances in CT and MRI, CT and MR venograms can evaluate cerebral venous system without invasive cerebral angiogram. However, cerebral angiogram may add many clues for diagnosis and also clear the potential questions from CT and MR venograms [3, 7, 12–16, 22] as seen in case 2. The variability of the cerebral venous system is evident in our review of 1500 cerebral angiograms, more than 68% demonstrate asymmetry of the dural sinus. The wide range of venous anomalies has traditionally been deemed clinically insignificant. But as we have shown in the examples above, venous drainages play an integral role in cerebral circulation and any aberrancy can result in a variety of clinical presentations from these venous anomalies. Our retrospective analysis of 162 cases with complete cerebral angiograms with good venous phase showed that an association exists between ruptured cerebral aneurysms and asymmetry of the dural sinuses. Asymmetry dural sinus was frequently seen in those cases with ruptured cerebral aneurysm. The relationship implies that asymmetry of dural sinus may play a role in the events leading to aneurysm rupture, presumably through increased venous pressures. Case 1 illustrated just one of many similar cases we have encountered a patient with ruptured cerebral aneurysm, hypoplasia of the left transverse and sigmoid sinuses and big cortical vein acting as collaterals to assist venous drainages. On the other hand, no clear association exists between non-ruptured cerebral aneurysms and symmetry of the dural sinuses. Among those 52 patients with incidental aneurysms, 21 of 52 had symmetry of dural sinus and 31 of 52 patients had asymmetry. Factors of aneurysmal rupture are many such as size, site, configuration and flow dynamics. We believe that the reason lies in the flawed assumption that non-ruptured aneurysms will never rupture, thereby making the analysis unreliable from our statistics. Those venous patterns may raise the possibility of venous hypertension to stir the cerebral circulation [1, 2, 8, 10, 17].

Dural sinus atresia is relatively rare in our series. Atresia dural sinus leads to chronic venous hypertension, increased intracranial pressure (ICP), and chronic headaches [1, 2, 8, 10, 17, 19]. Cortical veins eventually develop a tortuous corkscrew-type appearance. The corkscrew patterns of the cortical veins were compatible with a clinical history of chronic headaches and increased ICP. The symptoms of chronic venous hypertension, which may occur with dural sinus atresia or stenosis, depend on the collaterals and the location of atresia or stenosis. The venous outlet obstruction may result from not only hypoplasia and/or atresia but also stenosis [8, 10, 17]. Stenoses can occur at a variety of locations, such as at the transverse sinus as seen in case 1 and the sigmoid sinus as seen in case 2. In case 2, trigeminal neuralgia was attributed to arterial pulsations and irritating the 5^{th} cranial nerve despite a negative MRI and MRA. In actuality, numerous small venous channels causing nerve compression were discovered during surgery. Acute thrombosis of the left dural sinuses were induced from surgery and predisposed by underlying severe stenosis of the distal sigmoid sinus at the junction with jugular bulb. Angioplasty was necessary to dilate the stenotic segment and ensure the successful result of balloon assisted thrombectomy and thrombolysis. Not until the stenotic segment was dilated to a sufficient diameter did the recurrent thromboses cease to occur. Case 2 clearly illustrates not only the potential risk of dural sinus stenosis, but also how collaterals may compress upon the cranial nerves depending on the location. In case 2, findings of ventricular enlargement was thought to represent hydrocephalus but later recognized as a manifestation of chronic venous hypertension and white matter degeneration. MR venogram showed absence of left dural sinus, comparision with contrast MRI and hyperdensity of left transverse sinus on CT offer additional clues for thrombosis [12, 13]. In some cases, the diagnosis may require conventional angiogram with attention to venous phase and delay in cerebral circulation as seen in case 2. Dural sinus stenosis may occur at superior sagittal, transverse, and sigmoid sinuses, also occur distal to the dural sinuses as seen in case 2 and at the proximal jugular vein. Jugular vein stenosis has a potential leading to stasis of venous flow and induce thrombosis. Angioplasty and stenting were required to reopen the venous circulation after thrombolysis. Hyplplasia and stenosis are the most common entities among congenital variations, ectasia of dural sinus is rare and may associate with venous angioma. Ectasia of dural sinus may cause thrombosis due to stasis of venous flow.

There are many therapeutic options for acute dural sinus thrombosis. Literature indicated anticoagulation is the preferred treatment although, recent heparin trials at multiple international centers did show a long term improvement in the majority of cases with 57% complete recovery and 30% mild improvement. However,

there were 13% of severe deficit and 8.3% of death. In this series, there were only 37% of acute and 56% of subacute cases. Those high percent death indicated anticoagulation may not be sufficient to treat those acute thrombosis [9, 23–26]. We feel that anticoagulation may be tried first, however, thrombolytic treatment is indicated once imaging finding of venous congestion with hemorrhage and/or edema appears with worsening in clinical condition [22, 25, 26]. Balloon assisted thrombolysis and thrombectomy may be more effective than microcatheter direct thrombolysis alone [25].

Dural sinus thrombosis may be induced by surgery or trauma as seen in case 2. Traumatic dural sinus thrombosis may not be treated with thrombolysis due to acuteness of the injury with potential hemorrhagic complications [18]. Balloon assisted thrombectomy and stenting may be considered to recanalize the traumatic acute thrombosed dural sinus accessing the transverse and superior sagittal sinuses with optimal size and sufficiently flexible stent is difficult. Stenting may become more feasible for proximal transverse and superior sagittal sinuses in the near future [17, 20, 23, 29]. CT and catheter cerebral venogram may be better for follow up with stent cases because MR venogram tends to have artifacts [21].

It is well known that dural sinus AV fistulas are the result of sinus thrombosis [4–6]. It may lead to venous hypertensive encephalopathy from chronic venous hypertension. Treatment options for the dural sinus AV fistula included arterial embolization and sinus packing [4–6, 11, 20, 23, 27]. Arterial embolization of dural sinus fistula may not sufficient and prone to reoccur. Dural sinus packing of the dominant sinus would have created more venous obstruction and lead to severe venous hypertension [14]. Dural AV fistulas may be spontaneously thrombosed after stenting [23]. Stenting may be the third option to treat dural sinus AV fistula and the choice to resolve the venous hypertensive encephalopathy in those dominant sinus [4–6, 8, 11, 17, 19, 20, 23, 27].

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Acta Neurochir Suppl (2008) 101: 89–92

Printed in Austria

Transgenic rodent models of Parkinson's disease

B. K. Harvey, Y. Wang, B. J. Hoffer

Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD, USA

Summary

In the case of Parkinson's disease (PD), classical animal models have utilized dopaminergic neurotoxins such as 6-hydroxydopamine (6OHDA) and 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP). More recently, human genetic linkage studies have identified several genes in familial forms of PD. Transgenic models have been made that explore the function of PD-linked genes (e.g. α-synuclein, DJ-1, LRRK2, Parkin, UCH-L1, PINK1). Recent evidence suggests mitochondrial dysfunction may play a major role in PD. Manipulation of mitochondrial respiratory genes (e.g. mitochondrial transcription factor A or TFAM) also elicits a PD phenotype in mice. Transgenic mice (MitoPark) were developed that have TFAM selectively knocked out in dopaminergic neurons. The nigral dopamine neurons of MitoPark mice show respiratory chain dysfunction, accompanied by the development of intraneuronal inclusions and eventual cell death. In early adulthood, the MitoPark mice show a slowly progressing loss of motor function that accompanies these cellular changes. The MitoPark mouse enables further study of the role of mitochondrial dysfunction in DA neurons as an important mechanism in the development of PD. Transgenic technology has allowed new insights into mechanisms of neurodegeneration for a number of neurological disorders. This paper will summarize recent studies on several transgenic models of PD.

Keywords: Parkinson's disease; DJ-1; PINK1; Parkin; transgenic; mitopark.

Introduction

Parkinson's disease is emerging as a complex interplay of the environment and genetic risk factors. Overall, PD is primarily idiopathic with a subset (<15% of cases) with a family history of PD. In pedigrees with a pattern of inherited PD, genetic linkage studies have identified 13 PARK loci to date (OMIM 168600). Molecular genetics studies have identified genes associated with 7 of 13 PARK loci and we will be describing the current and possible transgenic animals for three of these genes (i.e. Parkin, DJ-1 and PINK1). We will also discuss a recently developed transgenic animal (MitoPark) that focuses on mitochondrial dysfunction as a pathogenic mechanism of PD.

Correspondence: Barry J. Hoffer, MD, PhD, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD 21224, USA. e-mail: bhoffer@intra.nida.nih.gov

Parkin (PARK2)

Studies of autosomal recessive inheritance pattern of early-onset PD in a group of Japanese families led to the identification of the Parkin gene at the PARK2 locus [24]. Additional studies have confirmed that mutations in Parkin are linked to autosomal recessively inherited PD. Unlike α-synculein that has few identified mutations, more than a 100 mutations have been identified in the Parkin gene [1, 18, 19, 26, 28, 29, 34]. Parkin has E3 ubiquitin-protein ligase activity [39] and targets proteins for degredation by the proteosome [8, 21, 46].

Several laboratories have generated Parkin knockout mice by targeting different exons of the Parkin gene [13, 22, 30, 33, 37, 45]. In mice missing exon 3, striatal dopamine levels are increased; synaptic excitability in striatal spiny neurons and DAT levels are decreased. However, the number of nigral dopaminergic neurons remains normal for up to 2 years. The mice exhibit behavioral deficits that are associated with the basal ganglia function and have decreased DA release in response to amphetamine [13, 22]. The exon 3 knockout mice show reduced mitochondrial respiration and increased oxidative damage [30]. Similar to exon 3 deletion, exon 7 deletion did not affect the nigral neuron numbers, but decreased TH-producing cells in the locus coeruleus [45]. In contrast, mice without exon 2 of Parkin exhibited no alterations in behavior, catecholamine levels or altered sensitivity to methamphetamine or 6-OHDA [32, 33]. Sato *et al.* [37] generated mice with a knockout of

exon 2 and identified age-related declines in striatal dopamine and increase in D1/D2 receptor binding using ex-vivo PET imaging. Behavioral testing and immunolabeling of dopaminergic nigral neurons revealed no abnormalities compared to wild-type mice [37]. Overall, Parkin knockout mice fail to develop a Parkinsonian phenotype, but the different knockout models may provide a means to examine the role of Parkin in protein turnover, oxidative stress and mitochondrial dysfunction.

DJ-1 (PARK7)

The DJ-1 gene was identified at the PARK7 locus [44] with a point mutation (L166P) that cosegregated with the disease allele in an Italian family [5]. PARK7, like PARK2 is inherited in an autosomal recessive manner. Many mutations in the DJ-1 gene have been associated with early onset PD [2, 3, 5, 15, 17]. DJ-1 is involved in multiple cellular processes including oxidative stress and cellular transformation [27].

Based on a mutation observed in human DJ-1 by Bonifati *et al.* [5], a transgenic mouse missing the first 5 exons and part of the promoter of DJ-1 was created [7]. No observable expression of DJ-1 was observed in the homozygous null mice which did show a progressive decline in selected motor tests. There was increased striatal dopamine and evoked dopamine overflow in the striatum. There was no change in the number of nigral dopaminergic neurons or markers of these neurons [7]. Similarly, by disrupting exon 2 of DJ-1, Goldberg *et al.* [14] generated mice with decreased evoked dopamine overflow in the striatum and lower locomotor activity compared to wild-type mice. No change in the number of dopaminergic neurons of the substantia nigra was observed [14]. A third study by Kim *et al.* [23] generated a DJ-1 knockout by also disrupting exon 2, the first coding exon of DJ-1, and found no change in striatal dopamine levels or nigral dopaminergic neuron numbers. These mice did exhibit decreased locomotion in response to amphetamine and increased sensitivity to MPTP which could be restored by viral vector delivery of DJ-1 to the striatum. Cortical neurons derived from embryonic brain of DJ-1 knockout mice were more sensitive to oxidative stress [23]. Overall, these studies demonstrate that absence of DJ-1 expression 1) decreases motor functions and 2) alters dopamine function in the nigrostriatal pathway. The DJ-1 knockout mice may provide a useful platform for testing gene therapeutic strategies for patients carrying deletion mutations and offer opportunities to study the function of DJ-1 in oxidative stress.

PINK1 (PARK6)

Analysis of the PARK6 locus on chromosome 1 [43] led to the identification of point mutations in the PINK1 gene, a putative mitochondrial kinase [42]. Mutations in PINK1 are the second most frequently occurring cause of autosomal recessively inherited early-onset PD [6, 16, 20, 35, 36, 40]. PINK1 is localized throughout the brain and colocalizes to mitochondria where it is thought to prevent mitochondrial dysfunction [12].

Recently, two studies describe knockdown [47] and knockout [25] of PINK1 gene in mice. First, Zhou *et al.* [47] used RNAi and the Cre-loxP system to induce expression of a PINK1 shRNA in the presence of Cre. Using CMV-Cre transgenic animals crossed with inactive PINK1 shRNA espression, they observed widespread silencing of the PINK1 gene in brain and other tissues. Despite decreased PINK1 mRNA and protein, no change in striatal dopamine, nigral dopaminergic neurons numbers and motor activity (rotarod test) was observed in the PINK1 knockdown mice compared to wild-type mice [47]. In the second study, Kitada *et al.* [24] created a PINK1 knockout mouse by deleting exons 4–7 (kinase domain) and introducing a nonsense mutation starting in exon 8. Mice deficient in PINK1 expression had normal levels of striatal dopamine and nigral dopaminergic neurons. Similar to observations of DJ-1 knockout mice, evoked dopamine overflow in the striatum is reduced in PINK1 knockout mice [25]. Mutations in both DJ-1 and PINK1 genes have been identified in subset of patients with early onset PD. Biochemical studies suggest DJ-1 stabilizes PINK1 and works cooperatively to protect cells against oxidative stress [41]. Studies with Drosophilia found that PINK1 may function through a similar pathway as Parkin as well [9, 31] Future studies examining the interactions of PINK1, Parkin and DJ-1 may lead to the development of a mouse model that more closely resembles the pathology of PD.

MitoPark mice

Indirect evidence suggests a role for mitochondrial dysfunction in sporadic PD [10]. In addition, studies of families with rare inherited forms of PD have identified genes involved in regulating mitochondrial function [9, 31, 38]. The hypothesis that mitochondrial dysfunction may be of etiological importance in PD has recently gained renewed attention because it has been shown that PD patients have an increased number of midbrain DA neurons with respiratory chain deficits compared to non-PD patients [4]. To experimentally test whether

the respiratory chain deficiency was a primary abnormality leading to inclusion formation and DA neuron death, or whether generalized metabolic abnormalities within the degenerating DA neurons cause secondary damage to mitochondria, a conditional knockout of the mitochondrial transcription factor A (Tfam) in DA neurons was created [11]. When crossed with a DAT-Cre transgenic mouse, these knockout mice (termed MitoPark mice) had reduced mtDNA expression and a respiratory chain deficiency in midbrain DA neurons. The knockout mice exhibited a Parkinsonian phenotype with adult onset of slowly progressive impairment of motor function accompanied by formation of intraneuronal inclusions and dopamine nerve cell death. Confocal and electron microscopy show that the inclusions contain both mitochondrial protein and membrane components. Overall, the MitoPark mice are a transgenic model of PD based on an underlying deficiency of the repiratiory chain in dopaminergic neurons of the midbrain. The MitoPark mice display several essential features of PD including 1) adult onset of neurodegeneration, 2) slowly progressive behavioral changes, 3) presence of intraneuronal inclusion (possibly a Lewy body equivalent), 4) preferential death of dopaminergic neurons in the SN compared to the VTA and 5) responsiveness to leva-dopa. The MitoPark mice may provide a useful model for testing potential therapies for the treatment of Parkinson's disease.

Concluding remarks

As mutations in human genes are identified and associated with neurodegenerative disease, transgenic models offer an opportunity to invasively study the mutant gene or combination of mutant genes and their role in the pathophysiology of the disease. More importantly, they provide a platform to evaluate potential genetic and pharmacological therapies.

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Acta Neurochir Suppl (2008) 101: 93–98

Printed in Austria

Nigrostriatal alterations in bone morphogenetic protein receptor II dominant negative mice

J. Chou[1], B. K. Harvey[1], T. Ebendal[2], B. Hoffer[1], Y. Wang[1]

[1] Neural Protection and Regeneration Section, National Institute on Drug Abuse, NIH, MD, USA
[2] Department of Neuroscience, BMC, University of Uppsala, Uppsala, Sweden

Summary

Background. We previously demonstrated that exogenous application of bone morphogenetic protein 7 (BMP7) reduced 6-hydroxydopamine-mediated neurodegeneration in a rodent model of Parkinson's disease. The purpose of this study is to examine the endogenous neurotrophic properties of BMP Receptor II in dopaminergic neurons of the nigrostriatal pathway.

Methods. Adult male BMPRII dominant negative (BMPRIIDN) mice and their wild type controls (WT) were placed in the activity chambers for 3 days to monitor locomotor activity. Animals were sacrificed for tyrosine hydroxylase (TH) immunostaining. A subgroup of BMPRIIDN and WT mice were injected with high doses of methamphetamine (MA) and were sacrificed for terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) histochemistry at 4 days after injection.

Results. BMPRIIDN mice had lower locomotor activity than the WT. There is a significant decrease in TH neuronal number in substantia nigra compacta, TH fiber density in the substantia nigra reticulata, and TH immunoreactivity in striatum in the BMPRIIDN mice, suggesting that deficiency in endogenous BMP signaling reduces dopaminergic innervation and motor function in the nigrostriatal pathway. Administration of MA increased TUNEL labeling in the substantia nigra in the BMPRIIDN mice.

Conclusions. Endogenous BMPs have trophic effects on nigrostriatal dopaminergic neurons. Deficiency in BMP signaling increases vulnerability to insults induced by high doses of MA.

Keywords: Bone morphogenetic protein; BMPRII; methamphetamine; apoptosis.

Introduction

Bone morphogenetic protein-7 (BMP7) is a trophic factor in the transforming growth factor (TGF)-β superfamily. Both BMP7 and its receptor are found in the nigrostriatal pathway in the CNS. BMP7 mRNA is strongly expressed in nigral area of adult rats [2]. Its receptor bone morphogenetic protein receptor type II (BMPR-II) is highly expressed in the dopaminergic neurons of substantia nigra and ventral tegmental area (VTA [9]).

The physiological function of BMP7 in nigrostriatal DA neurons has been studied in different laboratories. In rat mesencephalic cell cultures, BMP7 increased the number of tyrosine hydroxylase (TH) cells and dopamine uptake [7]. Intranigral delivery of BMP7 reduced motor deficits, prevented the loss of TH immunoreactivity in nigra, and restored dopamine (DA) release in striatum in 6-hydroxydopamine- lesioned rats [5]. BMP7 is also protective against other dopaminergic neurotoxins. Our recent studies show that BMP7, given exogenously, reduced methamphetamine (MA) -mediated toxicity in DA neuronal culture and in the substantial nigra *in vivo* [3]. These data suggest that BMP7 has trophic effects in the nigrostriatal DA pathway. The role of BMPRII in BMP7-mediated neuroprotection of the nigrostriatal system has not been determined.

A study by Althini *et al.* [1] found that mice homozygous for a truncated dominant-negative form of BMPRII (BMPRIIDN), targeted to the 3′UTR of the TH locus and expressed using an internal ribosomal entry sequence (IRES), exhibited reduced locomotor activity, low DA levels. There was reduced TH immunoreactivity in substantia nigra and striatum, as well as decreased norepinephrine (NE) levels in the submandibular gland. However, some of the effects were due to a Neo cassette present in the targeting construct. Removal of the Neo cassette (Neo-) normalized NE content in the submandibular gland and partially restored DA content in nigra and striatum in these

Correspondence: Yun Wang, M.D., Ph.D., National Institute on Drug Abuse, I.R.P., 5500 Nathan Shock Drive, Baltimore, MD 21224, USA. e-mail: ywang@intra.nida.nih.gov

mice. These data suggested that the expression of the BMPRIIDN at the TH locus without the Neo cassette may affect dopamine production in the striatum, but the quantitative effects on locomotor activity or on the TH levels in the nigra, striatum, and VTA were not measured [1]. In this study, we examined the function of BMPRII using the BMPRIIDN mice without a Neo cassette. We found that BMPRIIDN mice had reduced striatal and nigral tyrosine hydroxylase immunoreactivity, decreased locomotor activity and increased sensitivity to methamphetamine toxicity. Our data indicate that deficiency in endogenous BMP signaling increases vulnerability to insults induced by the dopaminergic neurotoxin methamphetamine.

Methods

Animals and drug administration

Adult male BMPRIIDN homozygotes with no neo cassette (Neo-) and wildtype (WT) controls were provided from Uppsala University [1].

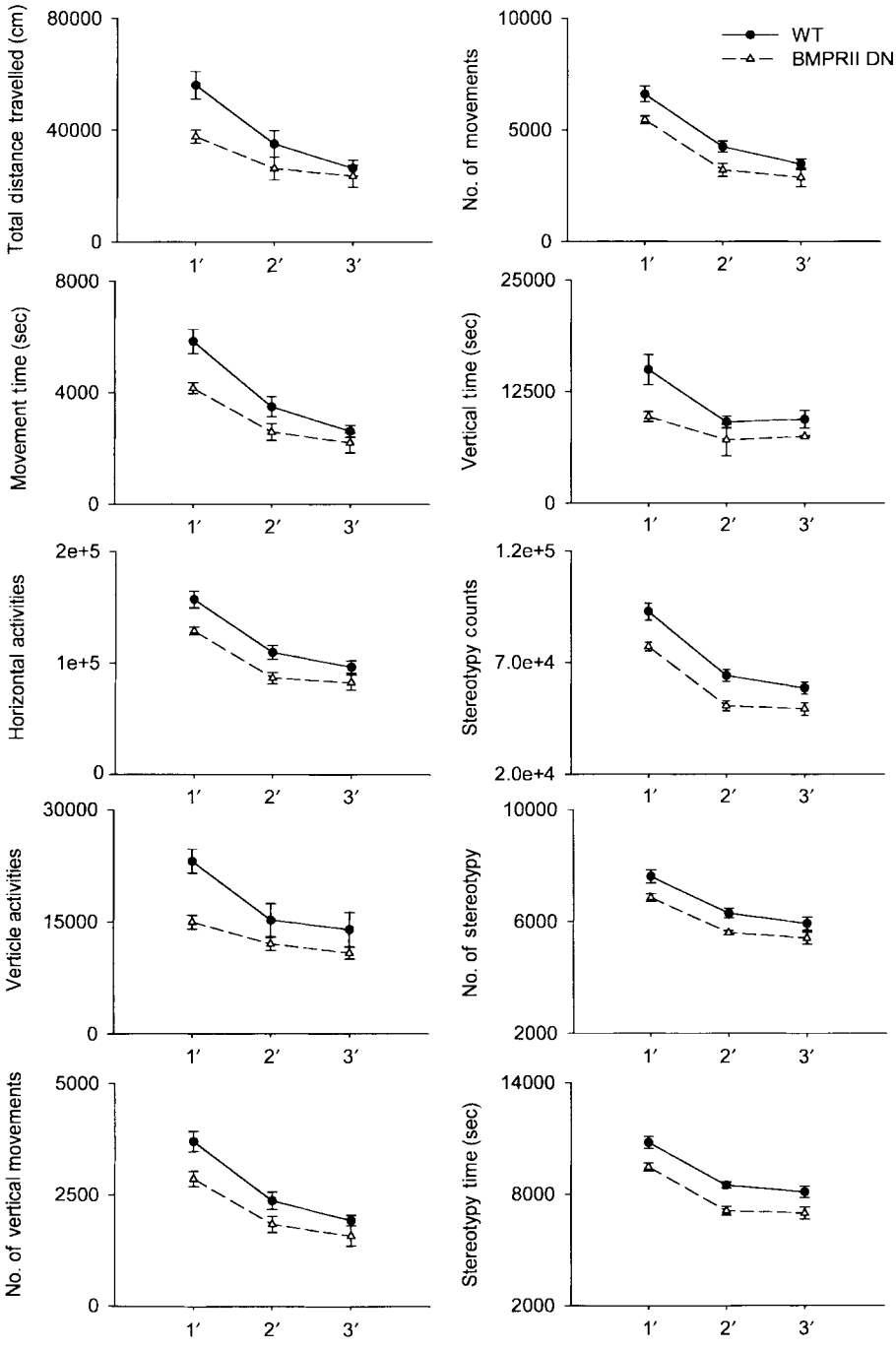

Fig. 1. Locomotor activity of BMPRIIDN and WT mice. Animals were individually placed in the activity chambers for 3 days. Ten different locomotor parameters were recorded daily. BMPRIIDN mice (*dashed tracing*) had a significant decrease in horizontal (total distance traveled, movement time, horizontal activity, number of movement, $p < 0.01$, two-way ANOVA), vertical movement (vertical activity, vertical time, number of vertical movement, $p < 0.05$, two-way ANOVA), and stereotypy (stereotype time, # of stereotypy, stereotypy counts, $p < 0.05$, two-way ANOVA) than the wild type mice (*solid tracing*)

Some animals were injected subcutaneously with 4 doses (2 h apart) of MA (10 mg/kg s.c.) or saline (0.01 ml/10 g, s.c.). During injection period, animals were housed individually without bedding.

Behavioral measurement

Mice were individually placed in infrared-beam locomotor chambers equipped with food, water and bedding for 72 h (Accuscan activity monitor, Columbus, OH). The vertical sensors were situated 10 cm from the floor of the chamber. Motor activity was calculated using the number of beams broken by the animals.

TH immunostaining

Mice were anesthetized with chloral hydrate (400 mg/kg i.p.) and perfused transcardially with saline followed by 4% paraformaldehyde in phosphate buffer (PB). Brain sections (25 µm) were rinsed in 0.1 M PB, blocked with 4% bovine serum albumin (BSA) and 0.3% Triton x-100 in 0.1 M PB. Sections were then incubated in a primary antibody solution (rabbit polyclonal anti-TH, 1:500, Chemicon, Temecula, CA) for 17–19 h at 4 °C. Sections were rinsed in 0.1 M PB and incubated in biotinylated horse anti-rabbit IgG (1:200; Vector Laboratories, Burlingame CA) for 1 h, followed by incubation for 1 h with avidin-biotin-horseradish peroxidase complex. Staining was developed with 2, 3′ diaminobenzidine tetrahydrochloride (0.5 mg/mL). Selective TH pixel density was obtained by subtracting the background density (in the parietal cortex) from the density in striatum.

Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL)

Animals were sacrificed 4 days after saline or MA administration and the brains were removed and sectioned (25 µm). A standard TUNEL procedure was performed as previously described [4]. Briefly, slide-mounted sections were rinsed in 0.5% Triton X-100 in 0.01 M PBS for 20 min at 80 °C. One hundred µL of the TUNEL reaction mixture was added onto each sample in a humidified chamber followed by 60 min incubation at 37 °C.

Statistics

Student's *t*-test, 1 or 2-way ANOVA + post-hoc Newman-Keuls test were used for statistical comparison. Data are presented as mean + S.E.M.

Results

Locomotor activity

Twenty-five BMPRIIDN mice and 25 WT controls were individually placed in the activity chambers for 3 days. Ten different locomotor parameters were recorded daily (Fig. 1). The highest locomotor activity in both BMPRIIDN and WT was observed in the first day. The movement was reduced in the 2nd and 3rd days, indicat-

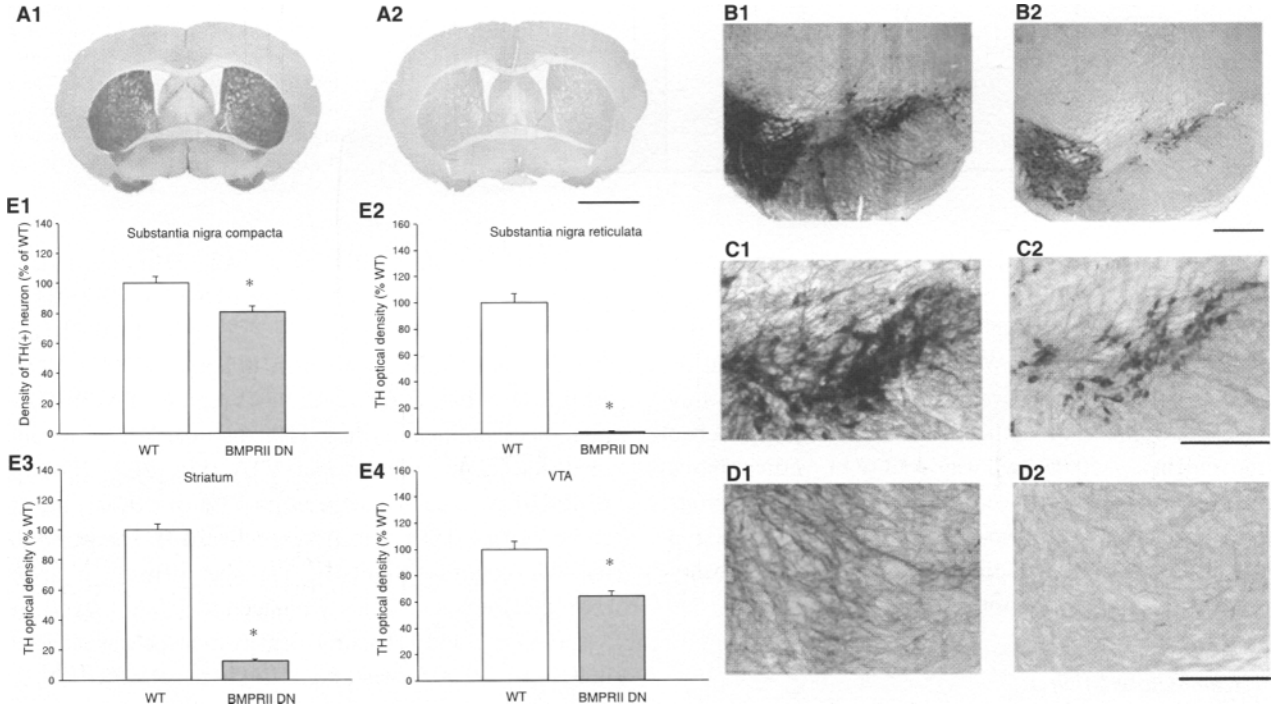

Fig. 2. BMPRIIDN mice exhibit decreased TH-immunoreactivity in nigra and striatum. Photomicrographs were taken from WT and BMPRIIDN mice. THir is reduced in striatum (WT: A1 *vs.* BMPRIIDN: A2), VTA (WT: B1 *vs.* BMPRIIDN: B2), SNpc (WT: C1 *vs.* BMPRIIDN: C2) in the BMPRIIDN mouse. Less THir fibers were also found in the SNpr in this animal (WT: D1 *vs.* BMPRIIDN: D2). Calibration: A: 2000 µm; B: 500 µm; C, D: 250 µm. (E) TH immunoreactivity is reduced in BMPRIIDN mice. Averaged THir was taken from 5 WT (*clear bar*) and 5 BMPRIIDN (*dark bar*) mice. THir and TH neuronal density were normalized by comparison to the mean of WT controls. In all regions, BMPRIIDN mice had significantly less THir than the WT ($^*p < 0.05$, *t*-test)

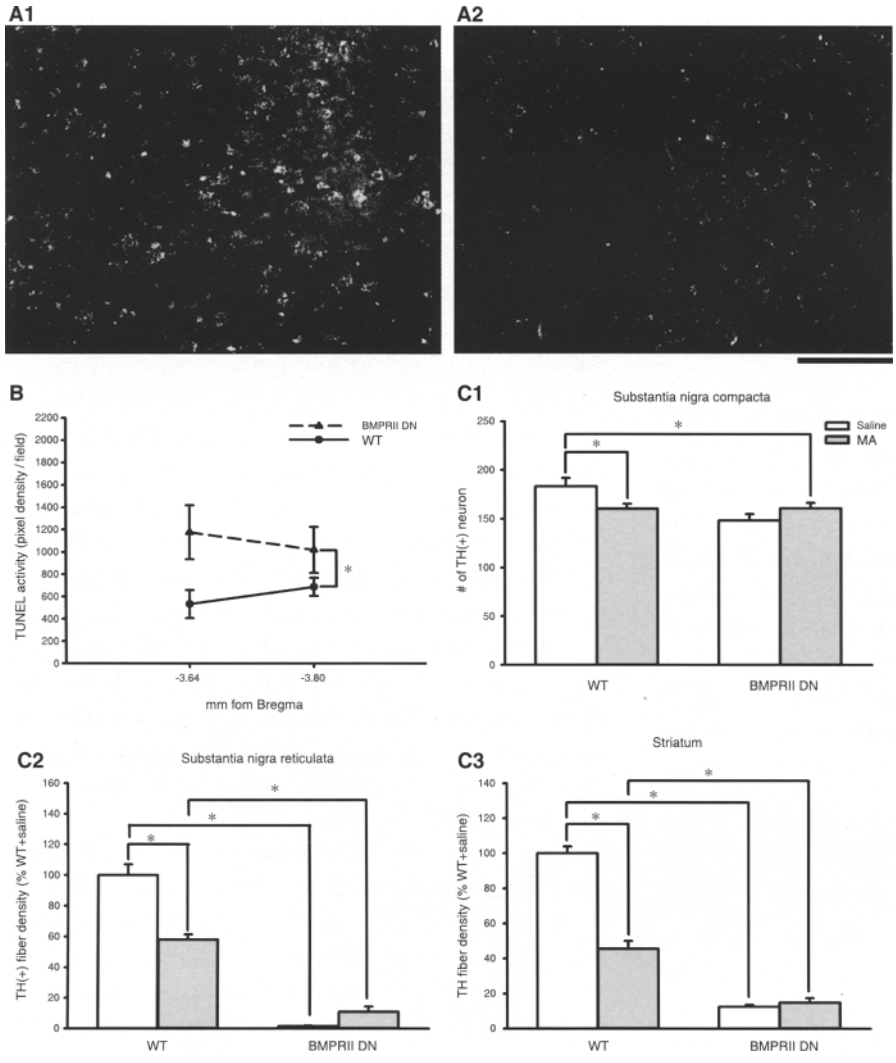

Fig. 3. High doses of MA altered TUNEL and THir in nigrostriatal pathway. BMPRIIDN (A1) and WT (A2) mice were sacrificed on the 4th day after MA administration (10 mg/kg, ×4). MA injection induced TUNEL labeling. There is an enhancement of TUNEL activity in SNpc (–3.64 mm to bregma) in the BMPRIIDN (A1), compared to the WT (A2). Calibration: 50 μm. (B) The optical density of TUNEL labeling was averaged in 2 regions in SNpc (AP to bregma: –3.64 and –3.80 mm). MA injection significantly increased TUNEL density in the BMPRIIDN mice ($p<0.05$, 2-way ANOVA). (C1–C3) THir in nigra and striatum after MA injection in BMPRIIDN and WT mice. THir was examined at 4th day after MA injection. MA significantly reduced THir in striatum and SNpr in the WT mice. There is no difference in THir in striatum and nigra with and without MA treatment in the BMPRIIDN mice ($^{*}p<0.05$, 1-way ANOVA)

ing that animals had adapted to the new environment. There was no difference in the time spent for adaptation between the BMPRIIDN and WT mice. BMPRIIDN mice, compared to the WT mice, had a significant decrease in horizontal movement (i.e. total distance traveled, movement time, horizontal activity, number of movements, $p<0.05$, two way ANOVA), vertical movement (vertical activity, vertical time, number of vertical movements, $p<0.05$, two-way ANOVA), and stereotypic behaviors (stereotype time, # of stereotypy, stereotypy counts, $p<0.05$, two-way ANOVA) (Fig. 1).

TH immunoreactivity

A total of 5 BMPRIIDN and 5 WT mice (or 10 samples for each group; left and right hemispheres from each section) were used for tyrosine hydroxylase (TH) immunostaining. TH immunoreactivity (THir) was quantitatively analyzed in 4 regions: THir optical density in striatum (WT: Fig. 2A1; BMPRIIDN: Fig. 2A2), THir optical density in VTA (WT: Fig. 2B1; BMPRIIDN: Fig. 2B2), THir neuron density in SNpc (WT: Fig. 2C1; BMPRIIDN: Fig. 2C2), and THir fiber density in SNpr (WT: Fig. 2D1; BMPRIIDN Fig. 2D2). In all these regions, BMPRIIDN mice had significantly less THir than the WT. THir optical density in striatum and VTA (Fig. 2E3, 2E4) of BMPRIIDN mice was reduced to 13% ($p<0.001$, t test) and 64% ($p<0.001$, t test), respectively, as compared to the WT controls. Similarly, TH fiber density in SNpr (Fig. 2E2) was significantly reduced to 1% ($p<0.001$, *t*-test, Fig. 2E2) and TH neuron density in SNpc was reduced to 81% ($p=0.004$, *t*-test, Fig. 2E1) in the BMPRIIDN.

Sensitivity to high doses of MA

i). TUNEL labeling: BMPRIIDN and WT mice were sacrificed for TUNEL labeling on the 4th day after MA or saline administration. TUNEL was examined in 2

regions in SNpc (AP to bregma: –3.64 and –3.80 mm). We found that saline administration did not induce TUNEL in BMPRIIDN and WT. MA injection enhanced the density of TUNEL activity in both BMPRIIDN ($n=5$) and WT animals ($n=7$, Fig. 3). There was an enhancement of TUNEL in the BMPRIIDN mice (BMPRIIDN: Fig. 3, A1 *vs.* WT: Fig. 3, A2). The optical density of TUNEL was further analyzed in all animals. MA injection significantly increased TUNEL labeling in the BMPRIIDN, compared to the WT (Fig. 3B, $p<0.05$, two way ANOVA).

ii) TH immunoreactivity: Five BMPRIIDN and 5 WT mice were injected with MA (10 mg/kg, ×4). MA-mediated changes in THir were examined at the 4th day after injection. MA significantly reduced THir in the striatum and SNpr in the WT mice. Since BMPRIIDN mice had very initial low basal TH innervation in striatum and nigra (Fig. 2E1–E3), administration of MA did not further attenuate the density of TH innervation in these regions. There was no difference in THir in the striatum and nigra with and without MA treatment in the BMPRIIDN mice ($p>0.05$, one-way ANOVA, Fig. 3C1–C3).

Discussion

In this study, we examined the trophic effects of BMPRII using dominant negative mice. We found that BMPRIIDN mice had reduced horizontal, vertical and stereotypic behaviors as well as less tyrosine hydroxylase expression in nigrostriatal pathway than the wild type controls. Previous reports have indicated that BMPRIIDN mice had less dopamine in nigra and striatum than the wild type [1]. Since the dominant-negative properties of the truncated BMPRII on BMP signaling were previously confirmed in cell culture (Althini *et al.* unpublished data), the change in dopaminergic function found in this and previous studies may be attributed to a deficiency in endogenous BMP signaling in the BMPRIIDN mice.

Our quantitative analysis indicates that TH neuronal fibers were more sensitive than cell bodies to the presence of the BMPRIIDN. TH fiber density in SNpr and striatum in the BMPRIIDN mice was reduced to 1 and 13% of the controls, respectively, whereas TH neuronal density was decreased only to 81%. The selective effect of BMPRIIDN on the TH-ir terminals is supported by finding that a BMPRII agonist selectively promotes dendritic growth from rat sympathetic neurons [8]. These data suggest that BMPRII has stronger trophic influence on DA neuronal fibers than on cell bodies of the midbrain DA neurons.

We have recently found that BMP7 is protective against dopaminergic neurotoxins in the nigrostriatal dopaminergic system. BMP7, given intracerebral, reduced 6-hydroxydopamine or MA-mediated loss of THir and behavioral deficits [3, 5]. BMP7−/+ mice, which have less BMP7 expression, are more sensitive to toxic effects of MA [3]. In this study, the sensitivity to high doses of MA was examined in WT and homozygous BMPRIIDN mice. Administration of MA reduced locomotor activity and THir in WT mice. In contrast, MA did not reduce the already low THir in striatum or nigra in BMPRIIDN mice. Although the locomotor activity could be suppressed by MA in the BMPRIIDN mice, no difference in horizontal, vertical and stereotypy behaviors between BMPRIIDN and WT mice was found after MA injection (data not shown). These data suggest that MA did not further reduce TH innervation or movement in the BMPRIIDN mice. The lack of response of nigrostriatal TH expression to MA may be attributed to a "floor effect", i.e. the near-complete loss of dopaminergic fibers in BMPRIIDN mice; THir was suppressed by more than 85% in striatum and SNpr in the absence of MA in these animals.

There is evidence that MA induces neuronal degeneration through activation of programmed cell death [4, 6]. In this study, we found that MA induced TUNEL labeling in WT and BMRPIIDN mice. There was a significant enhancement of TUNEL after MA injection in the nigra of BMPRIIDN animals. A similar observation was made in BMP7+/− mice after MA injection [3]. Our recent studies have indicated that there is minimal co-localization of TUNEL and THir after MA treatment in VM dopaminergic neuronal cultures. It is possible that the TH expression is suppressed in injured cells as loss of phenotype often precedes cell death. Current observations the BMPRIIDN mice and recent observations of the BMP7+/− mice, taken together, suggest that attenuation of endogenous BMP signaling increases MA-mediated degeneration in the nigrostriatal system.

In this study, we used BMPRIIDN mice which contain no Neo cassette [1]. These animals showed some reduction of DA levels in SN and striatum [1]. Mice with knock-in truncated ALK-2, another BMP receptor, did not have deficits in DA production. These data suggest that BMPRII is more important than ALK-2 in BMP regulation of DA synthesis. The ALK2DN mice were constructed using the same strategy as the BMPRIIDN mice where in the mutant receptor is expressed from an IRES downstream of the TH coding sequence. The ob-

servation that the ALK2DN transgenic showed no effect on DA production suggests that the effects from the BMPRIIDN mutation on DA production are not the result of targeting the construct to the TH locus. Further characterization of the BMPRIIDN animals is needed to rule out the possibility that the IRES-BMPRIIDN sequence added to the TH mRNA alters the levels of THir.

In conclusion, we found that BMPRII is important for TH expression and function in nigrostriatal dopaminergic neurons. Deficiency in BMPR increases vulnerability to MA injury. Our data suggest that activation of BMPRII by endogenous BMPs may mediate through trophic effects on nigrostriatal dopaminergic neurons in adult animals.

Acknowledgments

This work was supported by the Intramural Research Program at the National Institute on Drug Abuse, National Institutes of Health, USA.

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Acta Neurochir Suppl (2008) 101: 99–105

Printed in Austria

AAV-GAD gene for rat models of neuropathic pain and Parkinson's disease

J. Kim[1,2,*], **Y. S. Yoon**[1,*], **H. Lee**[3,4], **J. W. Chang**[1,2]

[1] Department of Neurosurgery, Yonsei University College of Medicine, Seoul, Korea
[2] Brain Korea 21 Project for Medical Science & Brain Research Institute, Yonsei University College of Medicine, Seoul, Korea
[3] Department of Microbiology, University of Ulsan College of Medicine, Seoul, Korea
[4] Research Institute for Biomacromolecules, University of Ulsan College of Medicine, Seoul, Korea

Summary

The introduction of therapeutic genes to neurons by genetic modification has potential as an effective treatment for CNS disorders for all that a successful clinical application has not yet been fully implemented. In this paper, we will discussed the role of AAV vectors with the GAD65 gene for animal models of PD and neuropathic pain. AAV vector is one of the most attractive gene delivery vehicles for direct introduction of therapeutic genes into the CNS in the treatment of neurological diseases. GAD65 is present as a membrane-associated form in synapses and is primarily involved in producing synaptic gamma-aminobutyric acid (GABA) for vesicular release. We constructed rAAV-GAD65 expressing rat GAD65 and demonstrated that rat Parkinsonian symptoms can be significantly improved concomitantly with the production of GAD65. We also demonstrated rAAV-GAD65 as a successful gene delivery vehicle in a chronic pain model by administrating rAAV-GAD65 to DRGs because GABA driven by GAD is a major inhibitory neurotransmitter in the dorsal horn of the spinal cord and also plays an important role in the ventral horn. We believe that AAV vectors can be excellent candidates for gene therapy of neurological diseases.

Keywords: Gene therapy; adeno-associated virus; glutamate decarboxylase 65; parkinson's disease; neuropathic pain.

Introduction

The narrow view of gene therapy, which inserts lost dielectric genes into somatic cells, had been technically developed to inclusive treatments strategy can be used to infectious or degenerative disease. One urgent factor to make gene therapy as a common method of treatment is to develop a gene transmitter that can deliver medical genes to target sites safely and effectively.

There are many different recombinant viral vector systems in use today in gene therapy. Efficient vector systems for transduction of neurons have been developed, such as recombinant adeno-associated (AAV) virus [42], adenovirus [2] and lentivirus [30]. This has been coupled with optimization of manufacturing methods for these vectors to produce pure, high-titer vector stocks suitable for use in the human brain[7], thus enabling infusion of a small volume into neuronal tissue to transduce a maximum number of cells. AAV vectors are excellent candidates for gene therapy of neurological diseases. The AAV-based vector system has been widely applied to neural systems, due to several advantages. First, they are safer because of non-pathogenic [29]. Second, they have a wide range of host cells. Third, they are able to deliver therapeutic genes to post-mitotic cells such as neurons [49], astrocytes [28] and oligodendrocytes [8]. Fourth, they provide sustained, long-term gene expression [29] that is required to treats chronic diseases. Some, such as rAAV2, are the most commonly used AAV serotype so far, efficiently transduces primary neurons in the central nervous system [5, 47].

Virus vectors can efficiently deliver genes to neurons and other neural cells *in vitro* and *in vivo*. These vector allow us to monitor neurobilogical functions, replace, correct, express or block expression of target genes, tag cell fate determination, and change the physiological state of specific cell populations. Gene transfer to the brain by using viral vectors offers the advantage of being less invasive than transplantation techniques, leaving the striatal circuitry undisturbed by cellular implants and eliminating risks of unwelcome host immune responses or tumor formation.

In this article, our brief review provided a description of AAV vector and we presented our research on

* These two authors contributed equally to this work.
Correspondence: Jin Woo Chang, M.D., Department of Neurosurgery, Yonsei University College of Medicine, CPO Box 8044, Seoul, Korea. e-mail: jchang@yuhs.ac

AAV-based gene therapy for treating PD and neuropathic pain.

Adeno-associated virus vectors for gene therapy

Adeno-associated viruses (AAVs) are small, non-enveloped, single-stranded DNA viruses of the parvovirus family [42]. The wild type AAV genome is 4.7 kb and integrates into the genome at a specific site on chromosome 19. No human disease has been associated with AAV infection. There are at least 7 serotypes known. Recently, there have been additional types recovered from mammalian tissue samples and some are currently being analyzed for their potential use as vectors [22]. Different serotypes infect tissues with varying efficiency. The serotype most commonly used for AAV vectors is serotype 2, which greatly infects the brain and retina, and has been used for a wide spectrum of applications targeting these organs [4, 10]. AAV1 also infects muscle tissue. As more and more AAV serotypes are being characterized and different serotype capsids can also be combined to generate novel tropisms, the potential for tissues that have not been easily infected with the current AAV serotypes may become amenable to AAV-based gene transfer in the future. Recent work supports the use of other AAV serotypes in brain-directed gene transfer. The properties of AAV4 and AAV5 differ from those of AAV2 as AAV5 diffuses more widely and AAV4 primarily transduces ependymal cells [11]. In the cerebellum, AAV5 transduces purkinje cells but not granule cells with high efficiency [1]. This is probably due to selective expression of the AAV5 receptor on specific neuronal types (J. A. Chiorini, unpublished data). Other serotypes of AAV might also show distinct tropisms when injected into the brain. Although AAV vectors are highly effective for gene delivery and are non-toxic, they have a relatively small transgene capacity (4–5 kb). This can be overcome by infection of cells simultaneously with 2 AAV vectors, which can recombine to generate a larger genome [13]. Studies on peripheral tissues show that transgenes are typically retained as extrachromosomal elements but they can also integrate randomly into the genome [9]. A number of clinical trials evaluating the use of AAV vectors for genetic and acquired diseases are currently underway. The brain is the target for monogenetic metabolic disorders, such as canavan disease [26], or degenerative CNS disorders including PD [27, 32] and chronic pain syndromes [17].

Recent studies on PD and neuropathic pain on AAV usage

PD is one of the most common neurodegenerative disorders characterized by rigidity, tremor, akinesia and gait disorder. The pathoanatomical basis for the predominant motor symptoms constitutes the loss of catecholaminergic neurons, especially dopaminergic neurons of the substantia nigra pars compacta (SNpc), in the adult brain at a pace far more rapid than in normal aging [14]. This cell death can take place over a period of 20 or more years, and the clinical symptoms of PD are not exhibited until a loss of up to 80% of striatal dopamine has occurred, representing a loss of up to 50% of dopaminergic cell bodies within the SNpc [20, 25]. Thus, gene therapy strategies involving transfer of genes encoding factors that increase dopaminergic cell phenotype and survival represent an innovative approach to attack this disease [32].

PD is particularly amenable to treatment using gene therapy strategies for several reasons: the identification of an active and preventable cell death process, within the substantia nigra (SN); the confinement of the initial pathology of the disease to discrete locations within the brain; the progression of the disease over a long time-frame; and neurodegenerative diseases like PD are chronic, and treatment options must be long-term or permanent. This makes PD particularly suitable for treatment with viral vectors, where a single application of a vectors can result in prolonged, stable transgene expression, with production of physiologically relevant levels of enzymes involved in the dopamine synthesis pathway or prolonged growth factor production over several months to promote reinnervation of the damaged nigrostriatal pathway [32]. An example is provided in a study by Luo *et al.* [36], who modified glutamatergic neurons of the subthalamic nucleus using AAV vector expression GAD in order to release inhibitory GABA in SNr. Other studies have demonstrated that a single injection of VEGF-expressing AAV vector into striatum improved the rotational behavior of rat PD models and promoted the survival of dopaminergic neurons and fibers [45].

In neuropathic pain, nearly half of all patients were unresponsive to currently available drugs. For those patients, gene therapy may be appropriate. The most widely studied gene therapy approach to treat experimental neuropathic pain has been the use of viral vector-based gene transfer. Viral vector gene therapy takes advantage of the natural ability of viruses to infect cells and have their genes expressed by host cells. Xu *et al.*

validated and demonstrated rAAV2 as a promising gene delivery vehicle in a chronic pain model by administrating rAAV2 encoding the opioid receptor gene to DRGs [50]. Exogenous proenkephalin, opiate receptor ligand, and gene transfer to the dorsal root ganglion (DRG) partially relieves pain symptoms [48]. Other studies have shown that rAAV2 transduces neurons in the DRGs as well as in the peripheral axon [21]. Long-term transgene expression is also sypported by rAAV2 in a variety of neural systems [6]. Additionally, Kwon *et al.* showed that viral-mediated transfer of the Brain-derived neurotrophic factor (BDNF) gene was successful at promoting a regenerative response in rubrospinal neurons following acute cervical spinal cord injury, with significantly less parenchymal damage than previously observed when infusing the BDNF protein [31].

Vector-based GAD gene therapy in Parkinson's disease and neuropathic pain GAD gene therapy for PD

In the current model of basal ganglia dysfunction in Parkinson's disease, nigrostriatal degeneration renders the subthalamic nucleus overactive with ensuing hyperactivity in the SN pars reticulata (SNr) and internal globus pallidus (Gpi). This in turn dampens motor output structures. Deep brain stimulation in the subthalamic

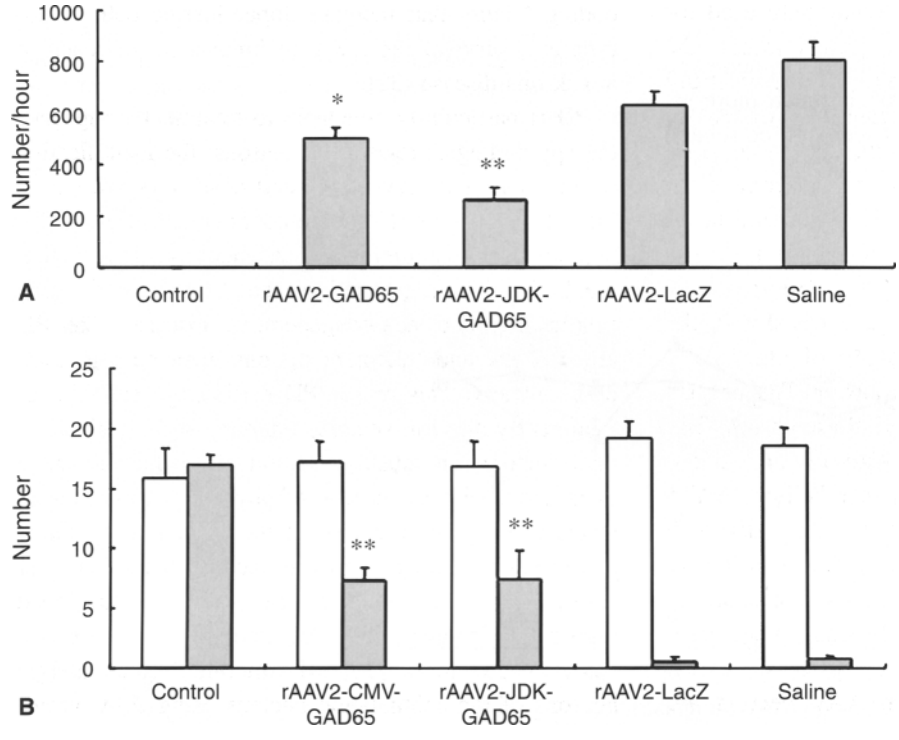

Fig. 1. Apormorphine-induced rotational behavial tests (A) and forepaw-adjusting stepping tests (B) in Parkinsonian rat models after injection of rAAV vectors into the STN. Bar graph indicates the number of ipsilateral (*gray bar*) and contralateral (*white bar*) steps. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$, compared to values from the PD group

Table 1. *General results from basal ganglia (STN, PPN and SNpr) neurons recorded in normal rats and in Pakinsonian rat models injected with rAAVs or vehicle*

	PPN			SNpr			STN		
	Neurons (*n*)	Mean firing rate (Hz)	Interspike interval (sec)	Neurons (*n*)	Mean firing rate (Hz)	Interspike interval (sec)	Neurons (*n*)	Mean firing rate (Hz)	Interval (sec)
Control	34	9.0 ± 2.3	0.20 ± 0.012	42	20 ± 1.3	0.04 ± 0.019	27	11 ± 1.0	0.15 ± 0.053
PD	24	19 ± 3.6	0.07 ± 0.016	50	30 ± 2.4	0.08 ± 0.037	10	16 ± 1.8	0.03 ± 0.007
rAAV2-Lacz	9	16 ± 2.0	0.05 ± 0.007	9	26 ± 3.9	0.03 ± 0.008	9	19 ± 2.0	0.01 ± 0.002
rAAV2-CMV-GAD65	37	15 ± 2.0	0.05 ± 0.007	40	21 ± 2.2*	0.03 ± 0.003	28	15 ± 1.2	0.05 ± 0.007
rAAV2-JDK-GAD65	47	10 ± 1.0*	0.07 ± 0.010	21	11 ± 1.4*	0.06 ± 0.007	45	9.0 ± 0.6*	0.05 ± 0.007

* $P < 0.05$, compared to values from the PD group.

nucleus (STN) curbing excitatory outflow from the STN is most successful in treating end-stage complications related to PD [15]. A similar down-regulation of non-physiological hyperactivity of the STN might be achieved pharmacologically by enhancing the level of the inhibitory neurotransmitter GABA, which is synthesized by glutamate decarboxylase (GAD). This hypothesis has been tested by the overexpression of AAV-GAD65/67 in the STN of rats later lesioned with 6-OHDA in the MFB [36]. Ad-GAD67-mediated transduction of cultured glial cells or LV transfer of GAD65/GAD67 in cultured astrocytes has been shown to enhance GABA release [18, 43]. Expression *in vivo* is stable for 4–5 months [36]. Whereas baseline GABA levels the STN are unchanged, local GABA release following electrical stimulation of the STN is increased four-fold and a shift in the majority of target neurons in the SNr from an excitatory to an inhibitory phenotype has been elicited [36]. AAV-GAD65 is much more effective than AAV-GAD67, and this seems to be related to lower expression levels of AAV-GAD67. AAV-GAD65-treated animals exhibit less apomorphine-induced rotation and behavioral side bias (head position bias, forelimb use). Even more importantly, 35% instead of 1% of dopaminergic cells in the SNpc survive following the 6-OHDA lesion in GAD65-expressing animals

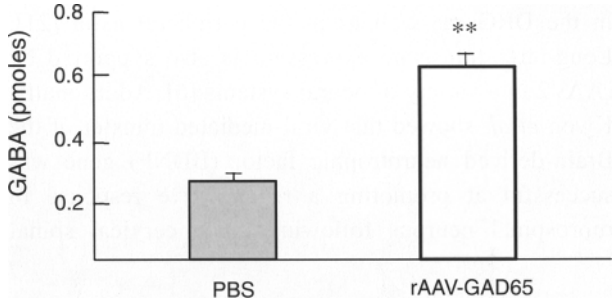

Fig. 2. Microdialysis and HPLC, the amount of GABA was estimated from the spinal cord fluid recovered from nerve terminals *in vivo*. Eight weeks after injecting rAAV-GAD65 or PBS into DRGs, GABA concentration was found to be statistically higher in rats with rAAV-GAD65 compared to the control rats. ** $P<0.01$, as compared with values from the vehicle group

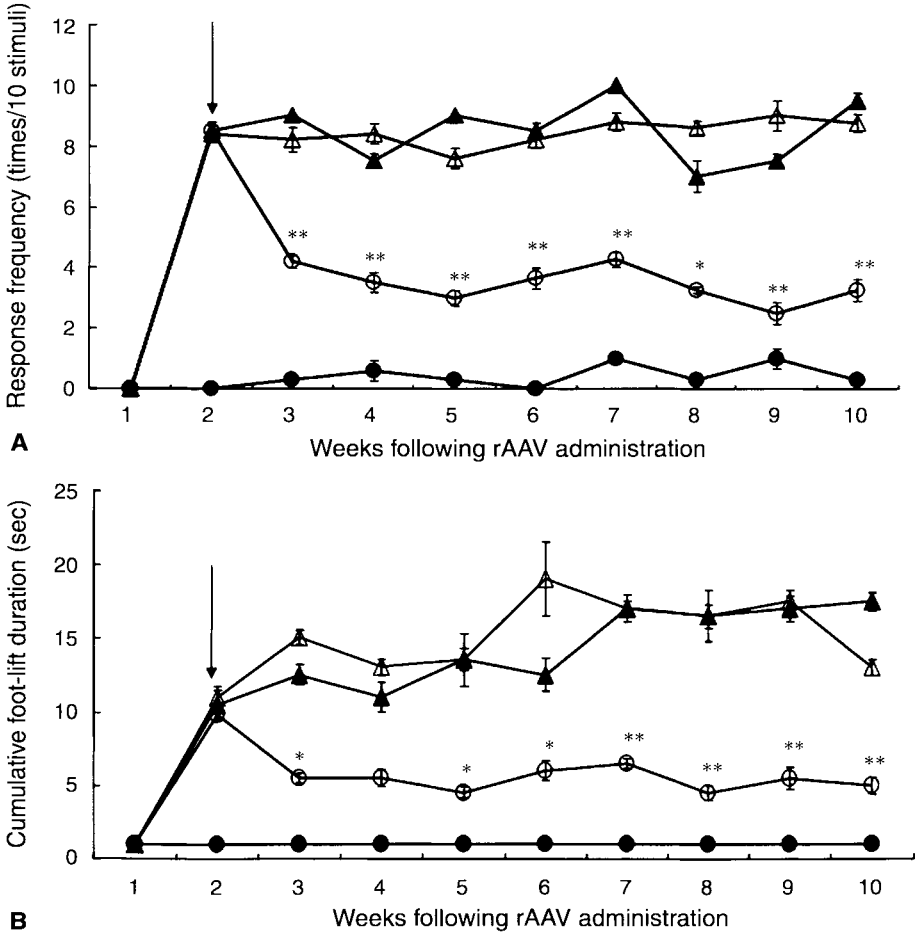

Fig. 3. Therapeutic effects of rAAV-GAD65 on neuropathic pain animal models. rAAV-GAD65 (2.4×10^6 infectious particles/ml, ○), rAAV-GFP (△), or PBS (▲). Normal control group had no operation (●). Once a week from 1 to 8 weeks post-injection, response rates to the *von Frey* filament (A) or pinprick (B) test were performed to monitor mechanical allodynia or hyperalgesia, respectively. ↓ rAAV injection point. An asterisk (*) indicates that the rAAV-GAD65 group differs significantly from the PBS-treated pain group at each time point. * $P<0.05$, ** $P<0.01$, as compared to values from the neuropathic pain group

[36]. Neuroprotection by GAD65/67 transfer has also been observed in chronically lesioned, aged rat [15]. We also reported that rAAV2-JDK-GAD65 was delivered to the STN exhibited significant behavioral improvements as compared to the saline-injected group (Fig. 1). According to electrophysiological data, the rAAV2-JDK-GAD65-injected group exhibited more constant improvements in firing rate compared to the PD group (Table 1) [34].

GAD gene therapy for neuropathic pain

Neuropathic pain is initiated or caused by primary lesions in or from the dysfunction of various neural systems and is potentially driven by multiple etiological factors [3]. Peripheral neuropathic pain caused by a wide spectrum of pathological processes consist of a number of phenomena occurring at different sites and times depending on disease states [12]. Among the complex mechanisms underlying neuropathic pain, partial nerve injury results in the loss of opiate-based or GABAergic inhibitory synaptic currents in the spinal cord. This then contributes to the phenotypes of neuropathic pain syndrome [40, 41]. Several studies have suggested that GAD expression and subsequent GABA production transiently attenuate neuropathic pain after spinal cord injury [35] and peripheral nerve injury [23]. GABA driven by GAD is a major inhibitory neurotransmitter in the dorsal horn of the spinal cord and also plays an important role in the ventral horn [46]. Two isoforms of mammalian GAD have been identified and are encoded by two distinct genes [19]. GAD65 is present as a membrane-associated form in synapses and is primarily involved in producing synaptic GABA for vesicular release. In contrast, GAD67 is distributed throughout the cell body and is mainly responsible for the production of cytosolic GABA by releasing GABA through a non-vesicular mechanism [37–39, 44]. The direct administration of rAAV-GAD65 to dorsal root ganglion induced constitutive GABA expression, which was readily detected by HPLC (Fig. 2). Both allodynic and hyperalgeic behavior tests suggested that neuropathic pain was noticeably reduced along with transgenic GAD65 expression (Fig. 3). Concomitantly, significant enhancement in GABA release following transgenic GAD65 expression was identified *in vivo* [33].

Conclusion

Gene therapy has several benefits compared to traditional therapy. Gene therapy offers the possibility of long-term expression of therapeutic proteins in specific cells, which is especially attractive when considering treatment options for chronic pain conditions such as PD and neuropathic pain.

Such as PD, it is a debilitating neurodegenerative disorder arising from loss of dopaminergic neurons in the SNpc and subsequent depletion of striatal DA levels, which results in distressing motor symptoms. Current mainstay treatments for PD, such as administration of L-dopa, treat motor symptoms but do little to alter the ongoing pathology. We observed that behavior improved when rAAV2-JDK-GAD65 was injected into the STN in rat PD models. According to electrophysiological data, the rAAV2-JDK-GAD65 group had improvements in firing rates [34].

In addition to neuropathic pain, it is initiated or caused by multiple etiological factors. Peripheral neuropathic pain has a common clinical problem with few existing treatments. Among the complex mechanisms underlying neuropathic pain, partial nerve injury induced loss of GABAergic neurons in the spinal cord. This phenomenon contributes to the neuropathic pain syndromes; therefore, our study provided evidence that GAD expression *via* AAV vector and subsequent GABA production attenuate neuropathic pain after peripheral nerve injury. Moreover, the magnitude of pain relief was maintained during the entire experimental period [24].

While animal studies involving cell-based therapies demonstrated potential, we feel that they can used in treating humans. Viral vector systems capable of efficiently transducing neurons, such as AAV, have been developed along with protocols for the manufacture of pure vector stocks suitable for application in human CNS. Based on GAD gene transfer to the subthalamic nucleus and dorsal root ganglion using an AAV vector, a clinical trial is has been set up to start recruiting patients [16]. The further disablement of the AAV vector and the use of combination of several different genes may ultimately result in a vector that can be used in patients with PD and neuropathic pain as a therapeutic alternative to surgery or traditional therapies.

Acknowledgements

This study was supported by a grant (M103KV010031-07K2201-03010) from Brain Research Center of the 21st Century Frontier Research Program funded by the Ministry of Science and Technology in the Republic of Korea. We also give thanks to Kyung Won Chang and Sung Jin Kim for their technical support.

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Acta Neurochir Suppl (2008) 101: 107–110

Printed in Austria

The role of genetic factors in the development of hemifacial spasm: preliminary results

I. B. Han*, N. K. Kim*, R. Huh, D. A. Shin, J. Y. Moon, H. M. Park, S. S. Chung

Department of Neurosurgery, Institute for Clinical Research, College of Medicine, Pochon CHA University, Seongnam, Korea

Summary

Hemifacial spasm (HFS) has been reported to result from vascular compression of the facial nerve at the root entry zone. The pathogenesis of HFS is not completely understood. Some study groups described that the vascular compression was due to the morphological changes of the vessel such as vertebral artery shifting. In this study, radiological evidence of VA shifting was identified in 26 (59.1%) of 44 patients with 3D-TOF MRA. We hypothesized that a genetic factor might be present for vascular change and tried to find out the role of a genetic factor more susceptible to vascular change causing vascular compression. We examined a single nucleotide polymorphism (SNP) in the genes related to vascular change such as methylenetetrahydrofolate reductase (MTHFR), thymidylate synthase enhancer region (TSER), endothelial nitric oxide synthase (eNOS), and vascular endothelial growth factor (VEGF) polymorphisms. 43 HFS patients and 207 healthy controls were genotyped and fasting plasma homocysteine (pHcy) concentrations were measured. The SNPs were genotyped using polymerase chain reaction (PCR) amplification followed by digestion with the restriction enzyme. The pHcy levels were not significantly different between HFS patients and controls. No association was detected between the SNPs in the selected genes and susceptibility to HFS. However, further study will be needed to confirm these findings.

Keywords: Polymorphism; hemifacial spasm.

Introduction

Hemifacial spasm (HFS) is characterized by tonic and clonic contractions of the muscles innervated by the facial nerve [1, 2]. It is generally believed that HFS is caused by vascular compression of the root entry zone (REZ) of the facial nerve [3, 4]. The pathogenesis of HFS remains poorly defined. Digre *et al.* found that 36 of 46 patients (78%) had a dolichoectatic vertebrobasilar artery, convex to the side of HFS in 33 (92%) [5]. Birbamer *et al.* found that 12 of 14 (86%) patients with HFS had abnormal vascular loops at the REZ [6]. In the previous our study, we determined that patients with HFS (48.6%) had more shifting of the vertebral artery (VA) than controls (13.5%). Therefore, it has been suggested that degenerative change of vessels may influence of displacement of the vertebrobasilar artery and play a role in the development of HFS [7].

Single nucleotide polymorphisms (SNPs) have been involved in stroke, coronary artery disease, or cancers and SNPs between human populations have made one population more susceptible to particular disease [8–16]. HFS does seem to be more common in patients with morphological changes of the vessel such as vertebral artery shifting, elongation, tortuosity or atherosclerosis and HFS occurs more frequently in persons of Asian origin [17]. Moreover, occasional familial cases have been described [18–20]. So, we hypothesized that there may be a correlation with vessel degeneration and the possible influence of genetic factors on development of HFS.

It has been reported that the SNPs of methylenetetrahydrofolate reductase (MTHFR), thymidylate synthase enhancer region (TSER), endothelial nitric oxide synthase (eNOS), and vascular endothelial growth factor (VEGF) gene are associated with vascular diseases such as stroke and coronary artery diseases [8–16]. Therefore, we examined SNPs of MTHFR, eNOS, TSER, and VEGF in a Korean population and tried to find out the role of a genetic factor more susceptible to vascular change causing vascular compression in patients with HFS.

*These two author contributed equally to this study.

Correspondence: Sang Sup Chung, M.D., Ph.D., Department of Neurosurgery, Pochon CHA University, 351 Yatap-dong, Bundang-gu, Seongnam 463–712, Korea. e-mail: nshanib@naver.com

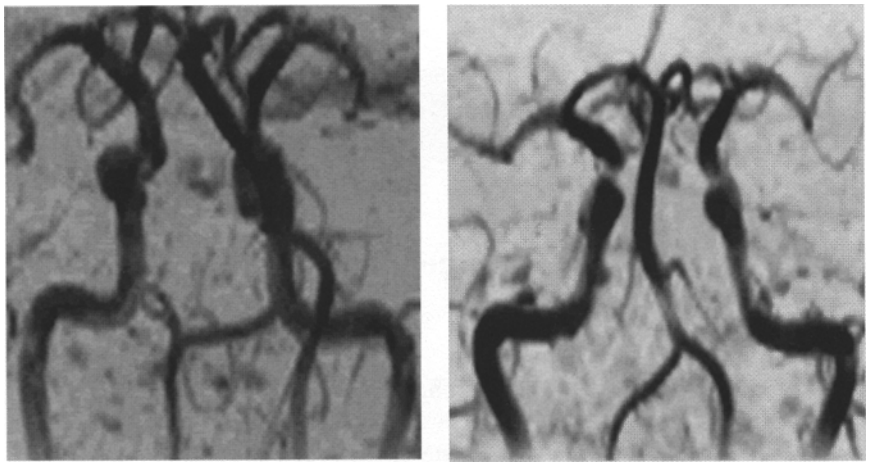

Fig. 1. 3D-TOF MRA illustrating the ectatic unilateral shifting of the vertebral artery. *Left*: Preoperative 3D-TOF MRA demonstrating a non-shifting of the vertebral artery. *Right*: If one vertebral artery deviates above the carotid system, it was regarded as a unilateral shifting of the vertebral artery

Materials and methods

Study population

The study population was composed of 43 patients with HFS and 205 control subjects. Patients with HFS were enrolled and recruited between October 2006 and July 2007 in the Bundang CHA Hospital. Patients with known past history of stroke or cardiovascular diseases were excluded. A preoperative magnetic resonance evaluation was performed using a 1.5-T superconducting magnet (Siemens Magnetom Symphony). The ectatic shifting of the VA was classified into two groups. If one VA deviated above the carotid system, it was regarded as a shifting of the VA. If not, it was regarded as non-shifting (Fig. 1). For control subjects, we selected healthy individuals matched for age from those presenting at our hospital for a health examination during the same period, and who were free from a recent or past history of cerebrovascular disease or of myocardial infarction.

Detailed information on past medical history was obtained from all study subjects. The institutional review committee of Bundang CHA Hospital approved this study in March 2006. Informed consent was obtained from all participants.

Biochemical measurements

Overnight fasting (12 h) blood samples were collected in EDTA-containing tubes, and placed on ice immediately. After centrifugation at 2000 rpm for 15 min, plasma samples were kept at −20 °C until analysis. Plasma homocysteine levels were determined by fluorescence polarization immunoassay (IMx, Abbott Laboratories).

Genetic analysis

Genomic DNA was extracted from leukocytes by using a DNA extraction kit (QIAmp blood kit, Qiagen) according to the protocol of the manufacturer. For the nucleotide 677 polymorphism, the primers 5′-GCA CTT GAA GAG AAG GTG TC-3′ (forward) and 5′-AGG ACG GTG CGG TGA GAG TG-3′ (reverse) were used, and for the nucleotide 1298 polymorphism, 5′-CTT TGG GGA GCT GAA GGA CTA CTA C-3′ (forward) and 5′-CAC TTT GTG ACC ATT CCG GTT TG-3′ (reverse) were used. Human genomic DNA (200 ng) was amplified with 100pmol of each forward and reverse primer, 1.5 mM $MgCl_2$, 0.2 M each deoxynucleotide triphosphate, and 1 unit *Taq* polymerase (Takara, USA) in a total volume of 100 µl. PCR conditions were as follows: denaturation at 94 °C for 5 min, followed by 35 cycles at 94 °C for 30 sec, 51 °C for 30 sec, and 72 °C for 30 sec, and a final terminal elongation at 72 °C for 5 min. PCR products were digested with *Hin*fI (for nucleotide 677) or *Fnu*4HI (for nucleotide 1298) for 2 h at 37 °C. Amplification success was monitored by 3.0% agarose electrophoresis. For the nucleotide 677, an undigested PCR product (203 bp) indicated a homozygous wild-type, three bands of 203, 173, and 30 bp indicated the heterozygous genotype, and two bands of 170 and 30 bp indicated the homozygous genotype. For nucleotide 1298, a single band of 138 bp indicated a wild-type, and two fragments of 119 and 19 bp indicated the homozygous genotype.

For identification of TSER genotypes, DNA was extracted from leucocytes with DNA extraction kit (QIAmp blood kit, Qiagen) according to manufacturer's protocol. Genomic DNA, which was dissolved TE (Tris-Cl 10 mM pH 8.0, EDTA 1 mM), was amplified with a Perkin-Elmer 2400 thermocycler as follows. Initial denaturation step was for 40 sec (s) at 94 °C followed by 30 cycles of denaturation for 30 sec at 94 °C, annealing for 60 sec at 62 °C, and elongation for 40 sec at 72 °C. The final elongation step was for 5 min at 72 °C. PCR primer sequences were 5′-GTG GCT CCT GCG TTT CCC CC-3′ for sense primers and 5′-GCT CCG AGC CCG GCC ACA GGC ATG GCG CGG-3′ for antisense primer. The PCR products were separated on 3% agarose gel by electrophoresis and then digested by the enzyme HinfI (10 unit/reaction mixture, MBI Fermantas). The DNA fragments were stained with ethidium bromide and viewed under UV light. The TS gene had a tandem repeat polymorphism (two repeats (2R) or three repeats (3R)). Homozygotes for the double repeat (2R2R) produced a singlet 214 bp band. Heterozygotes (2R3R) produced 214 bp and 242 bp fragments, and homozygotes for the triple repeat (3R3R) produced a 242 bp fragment.

eNOS 894G > T and VEGF 936C > T were also amplified by PCR and PCR products were digested with *Van*II and *Nla*III, respectively.

Statistical analysis

To estimate the relative risk for HFS for the various genotypes, an odds ratio (OR) and 95% confidence interval (CI) were calculated. Differences between the patient and control groups were assessed by the χ^2 test for categorical variables (sex, hypertension, and diabetes mellitus) and the two-sample *t*-test for continuous variables (age and pHcy level). For the multivariate analysis, logistic regression analysis was used to adjust for possible confounders, including age, sex, hypertension, and diabetes mellitus. The analysis was performed using GraphPad Prism 4.0 (GraphPad Software Inc., San Diego, CA, USA).

Results

Table 1 shows the distributions of clinical characteristics of patients with HFS and control subjects. Patients did not have a significantly higher prevalence of hyperlipid-

Table 1. *Baseline characteristics in hemifacial spasm (HFS) patients and control subjects*

	Control (%)	HFS (%)
Male (%)	85 (41.6)	8 (18.6)
Age (years, mean ± SD)	53.55 ± 11.75	51.83 ± 9.16
tHcy (μmol/L, mean ± SD)	9.503 ± 2.899	8.837 ± 8.249
Folate (nmol/L, mean ± SD)	9.845 ± 6.613	9.702 ± 5.994
Hypertension (%)	104 (50.6)	13 (30.2)
Diabetes mellitus (%)	37 (18.1)	6 (13.95)
Hyperlipidemia (%)	38 (18.4)	14 (32.8)
VA shifting (%)	30 (14.7)	23 (53.1%)

tHcy Plasma total homocysteine, *VA* vertebral artery.

Table 2. *Prevalence of each MTHFR, TSER, eNOS and VEGF genotypes between hemifacial spasm (HFS) patients and control subjects*

Genotype	Controls (%)	Cases (%)	OR	95% CI	*p*
MTHFR 677 C>T					
CC	69 (33.7)	14 (32.6)			
CT	106 (51.7)	24 (55.8)	1.116	0.540–2.306	0.855
TT	30 (14.6)	5 (11.6)	0.821	0.271–2.487	1.000
MTHFR 1298 A>C					
AA	143 (69.8)	36 (83.7)			
AC	58 (28.3)	6 (14.0)	0.411	0.164–1.028	0.055
CC	4 (2.0)	1 (2.3)	0.993	0.108–9.163	1.000
TSER					
3R3R	135 (67.2)	28 (65.1)			
2R3R	56 (27.9)	13 (30.2)	1.119	0.541–2.318	0.851
2R2R	10 (5.0)	2 (4.7)	0.964	0.200–4.645	1.000
eNOS 894 G>T					
GG	175 (82.2)	40 (93.0)			
GT	38 (17.8)	3 (7.0)	0.345	0.102–1.176	0.108
VEGF 936 C>T					
CC	140 (68.3)	31 (72.1)			
CT	58 (28.3)	9 (20.9)	0.701	0.314–1.564	0.445
TT	7 (3.4)	3 (7.0)	1.935	0.474–7.909	0.401

OR Odds ratios, *MTHFR* methylenetetrahydrofolate reductase, *TSER* thymidylate synthase enhancer region, *eNOS* endothelial nitric oxide synthase, *VEGF* vessel endothelial growth factor.

emia, diabetes mellitus or hypertension, compared to the controls. To evaluate the pure effects of the genetic polymorphisms on HFS, we adjusted the OR for age, sex, hypertension, and diabetes mellitus. Neuroimaging evidence of VA shifting was identified in 26 (59.1%) of 44 patients with 3D-TOF MRA. There is a statistically significant relationship between HFS and VA shifting in the ipsilateral cerebello-pontine angle ($p = 0.004$). The pHcy concentrations were not significantly different between controls and patients. There was no statistical difference in relation to the pHcy levels according to the different genotypes. No association was detected between the SNPs in the selected genes and susceptibility to HFS (Table 2). We cannot confirm a genetic role in the development of HFS.

Discussion

Vascular compression of the facial nerve by an ectatic vessel has been demonstrated to be the most common underlying etiology of HFS [1, 3, 4, 21, 22]. The vascular abnormality is usually an atherosclerotic aberrant or ectatic intracranial artery, most commonly the anterior or posterior cerebellar artery or the VA. Therefore, we hypothesized that some HFS patients may be genetically predisposed to vascular change causing subsequent compression of the facial nerve.

We selected MTHFR, TSER, eNOS, and VEGF genes because previous our studies showed the association between these genes and vascular disease such as ischemic stroke or coronary artery disease [8, 9, 16]. MTHFR are the main regulatory enzymes for homocysteine metabolism. Thymidylate synthase (TS) also competes with MTHFR for their common cofactor, 5,10-methylenetetrahydrofolate (5,10-me THF). Endotheilum-derived nitric oxide (NO) is synthesized from L-arginine by endothelial nitric oxide synthase (eNOS) encoded by the eNOS3 gene on chromosome 7. VEGF is a potent angiogenic factor. Previous our studies have shown that the MTHFR polymorphism represents genetic risk factors for ischemic stroke and eNOS polymorphisms are associated with coronary artery disease with adjustments for cardiovascular risk factors in a Korean population [8, 9, 16].

The common polymorphism in the MTHFR 677C>T can reduce enzyme activity, resulting in hyperhomocysteinemia, and can also increase the risks of cardiovascular diseases, certain types of cancer, and birth defects. The MTHFR 1298A>C polymorphism has also been found to reduce MTHFR enzyme activity, to a lesser extent than those with the 677C>T mutation, but conflicting results have been reported with respect to the association between 1298A>C polymorphism and pHcy levels. It has been reported that the MTHFR 1298A>C polymorphism may be associated with ischemic stroke, and may also play a protective role against colorectal cancer and acute lymphocytic leukemia.

It has been reported that there are ethnic variations in terms of the genetic polymorphism, as well as a difference in the occurrence of vascular disease between the Asian population and the Caucasian population. It is conceivable that the contributions of genetic polymorphisms to vascular disease may vary in different ethnic groups. The causes of HFS are multifactorial, and additional environmental risk factors of HFS may develop with age. Therefore, we adjusted for possible confounders such as age, hypertension, and diabetes mellitus. It

is not clear whether there is a casual relationship between genetic polymorphisms and HFS.

In this study, we demonstrated that the majority (53.1%) of patients with HFS had VA shifting, that VA shifting was significantly more common in HFS patients than in control. However, the results of our study did not show significant differences between the SNPs in the selected genes and susceptibility to HFS. We also found no association of genotypes with the pHcy levels. Contrary to previous studies of stroke, the pHcy levels were higher in controls than in HFS patients, but it did not reach statistical significance.

This study has limitations because it was conducted in a hospital-based population. The other possible limitation is relatively small the populations studied. Thus this study may have been underpowered for identifying effects of genotypes. Large, community-based random sampling is needed in order to resolve these limitations. Additional investigations with a standardized methodology involving large populations are still pending and might confirm the importance of genetic factors in HFS patients. Despite these limitations, this study is unique in that it focused on the relationship between the genetic polymorphisms and HFS in a Korean population and this study is the first to investigate an association between HFS and the genetic polymorphisms.

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Acta Neurochir Suppl (2008) 101: 113–117

Printed in Austria

Neurotrauma research in Taiwan

J. W. Lin[1,2], C. M. Lin[1,2], J. T. Tsai[3,4], K. S. Hung[1], C. C. Hung[1], W. T. Chiu[1,2,5]

[1] Department of Neurosurgery, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan
[2] Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[3] Institute of Biomedical Engineering, National Yang-Ming University, Taipei, Taiwan
[4] Department of Radiation-oncology, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan
[5] Graduate Institute of Injury Prevention and Control, Taipei Medical University, Taipei, Taiwan

Summary

Because of the rapid industrial and economic growth, Taiwan and other developing countries have faced an enormous increase in the number of motorcycles, which has subsequently caused a rapid increase of the motorcycle-related traumatic brain injuries (TBI). In order to tackle this serious problem, stepwise approaches for TBI were implemented in Taiwan from 1991 to 2007.

Step 1 was to do a nationwide TBI registry in order to identify the risk factors and determinants. We found that the major cause of TBI in Taiwan was motorcycle-related injury, and very few motorcyclists wore a helmet. Step 2 was to launch the implementation of the helmet use law on June 1, 1997. A rapid decline of TBI hospitalizations and deaths was demonstrated soon thereafter. Step 3 was to enroll into international collaborations with the Global Spine and Head Injury Prevention Project (Global SHIP Project) groups for TBI. The comparative results thus obtained could be used to develop prevention strategies for developing countries. Step 4 was to implement clinical researches for TBI, which included a Propofol study, hyperbaric oxygen therapy (HBOT), brain parenchymal oxygen ($PbtO_2$) monitoring, etc. Step 5 was to develop guidelines for the management of severe TBI in Taiwan. Through a 2-year period of review, discussion, and integration, a 9-chapter guideline was published in June 2007. In summary, our experience and process for management of TBI in Taiwan can be used as a reference for other developing countries.

Keywords: Traumatic brain injuries; motorcycle injury; helmet use law; injury prevention.

Introduction

Among accidental injuries, traumatic brain injury (TBI) is regarded as the most important cause of death. About half of the injury deaths are related to TBI. Before 1997, Taiwan was one of the areas with the highest incidence and mortality rate of TBI in the world. This situation mainly resulted from a large number of motorcyclists, of whom only very few wore a helmet [4, 24]. However, after the mandatory helmet use law was enforced, there was a drastic improvement in injury deaths [1, 15]. The researches and management of TBI in Taiwan started from epidemiological studies, intervention, and then gradually stepped into the field of clinical trial and development of TBI treatment guidelines. We hope that our 26-year experience with stepwise approaches for the prevention and treatment of TBI can be used as a reference for other developing countries.

Correspondence: Wen-Ta Chiu, M.D., Ph.D., Department of Neurosurgery, Taipei Medical University-Wan Fang Hospital; Graduate Institute of Injury Prevention and Control, Taipei Medical University; 111, Section 3, Hsing-Long Road, Taipei 116, Taiwan. e-mail: wtchiu@tmu.edu.tw

Step 1: epidemiological study of traumatic brain injury

A total of more than 160,000 TBI patients were collected over the past 20 years (Fig. 1) [2–4, 6, 9, 11–13, 16–19, 21–24, 30]. From the period of 1987 to 1991, the incidence rate of TBI in the urban area – Taipei City was $220/10^5$, the mortality rate was $22/10^5$, 47% of TBI were caused by traffic injuries, and 56% of traffic injuries were motorcycle related, whereas in the rural area – Hualien County, the incidence rate of TBI was $380/10^5$, the mortality rate was $88/10^5$, 79% of TBI resulted from traffic injuries, and 66% of traffic injuries were motorcycle-related (Fig. 2) [20].

From 1991 to 1993, over 24,000 cases of head injury were collected from 4 counties of Eastern Taiwan and adjacent island: Ilan County, Hualian County, Taitung County, and Penghu Island (Table 1). The final results of incidence rates of TBI from Ilan County, Hualian

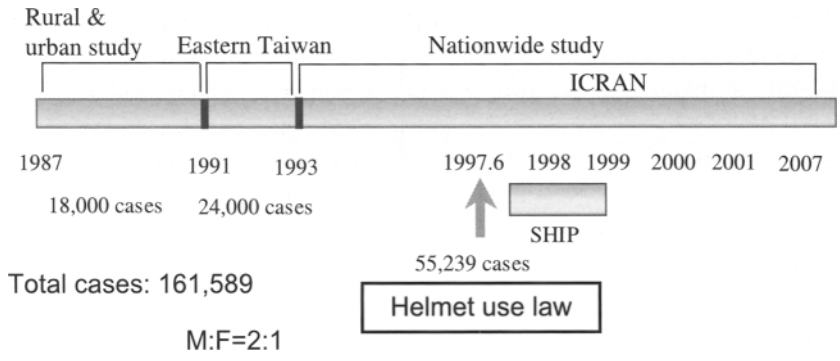

Fig. 1. Epidemiological study of TBI in Past 20 Years

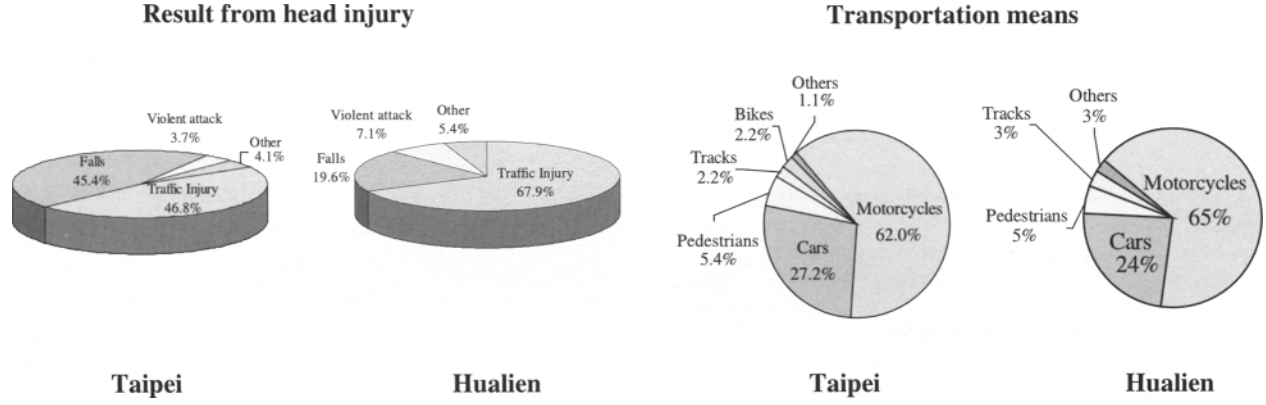

Fig. 2. Comparative study of TBI in Taipei City and Hualian county

Table 1. *Epidemiological study of TBI in eastern Taiwan and adjacent island*

Regions	Incidence rate	Mortality rate	Traffic injury related incidence (%)
Ilan county	311/100,000	53/100,000	60
Hualien county	437/100,000	72/100,000	61
Taitung county	341/100,000	83/100,000	54
Penghu county	260/100,000	84/100,000	74

County, Taitung County, and Penghu Island were $311/10^5$, $437/10^5$, $341/10^5$, $260/10^5$, and the mortality rates were $53/10^5$, $72/10^5$, $83/10^5$, $84/10^5$, respectively. Traffic injuries accounted for 60%, 61%, 54%, and 74% of TBI, respectively. The survey indicated that the incidence and mortality rates of TBI in Eastern Taiwan and island Counties were higher than in Taipei City.

From 1993 to 1997, a nationwide study from 56 hospitals was conducted, which showed that average incidence rate was $230/10^5$ from the database of about 50,000 patients, 69% of whom were related to traffic injury, and 70% of traffic injuries were caused by motorcycle injuries.

From our epidemiological studies, we conclude that: 1) the incidence of TBI was higher in the rural area than in the urban area; 2) the major cause of TBI was traffic injury; 3) the most common cause of traffic injury was motorcycle related injury; 4) most of the motorcycle riders did not wear a helmet. So we asserted that the mandatory helmet use law would be the most important and effective policy to reduce and to prevent TBI in Taiwan [2, 4, 6, 12, 13, 16–21, 23, 24, 32].

Step 2: intervention

Nowadays motorcycles have become the most common and most important transportation vehicles in Taiwan. Since the implementation of the helmet use law in June 1997, helmet wearing has been required for all the motorcycle riders (including drivers and passengers). In order to clarify the effectiveness of the mandatory helmet use law, we collected 9860 motorcycle related TBI patients from 7 major hospitals in Taiwan between June 1st, 1994 and January 31st, 1998. Comparing the condition before and that after the mandatory helmet use law, we found that after the helmet use law there was a 17.4% decrease in the rate of motorcycle related TBI, a shorter hospitalization period, less severity of the injury, and better prognosis. Furthermore, the rate of disturbed

consciousness in these motorcycle related TBI was reduced by 15%, and the skull fracture and intracranial hemorrhage were reduced by 10–20%. All of these results were statistically significant ($P<0.001$). It also showed that a motorcycle rider without a helmet carried a 7.08 times higher risk to have severe TBI than with a helmet [1, 14].

Due to above positive results, we carried out another nationwide survey from June 1, 1996 to May 31, 1998. We collected data on 8795 cases of motorcycle-related head injuries from 56 major Taiwanese hospitals, and compared the situation 1 year before and immediately after implementation of the helmet use law. After implementation of the law, the number of motorcycle-related head injuries decreased by 33%, from 5260 to 3535. A decrease in the length of hospital stay, severity of injury, and better outcome were also seen. The likelihood ratio χ^2 test showed that severity decreased after implementation of the law ($P<0.001$). Furthermore, full helmets were found to be safer than half-shell helmets [15].

According to the reports from the Bureau of National Health Insurance, traffic injuries-related in-patient medical expenditures were reduced by one hundred and ten million US dollars in average per month after implementation of the mandatory helmet use law. The data from the Transportation Bureau showed that the numbers of motorcycle-related deaths were reduced by 423 persons per month as compared with the same duration before the legislation. The data from the Department of Health, Executive Yuan, ROC also showed the same tendency. From all of these data, we proved that helmet wearing is very effective not only in dramatic reduction of the mortality rate and severity of head injury, but also in greatly decreased medical expenditure.

Conclusions from our helmet use law intervention included; 1) a decrease in the number of TBI, 2) a decreased in the rate of intracranial hemorrhage, 3) a decreased in the number of cranial operations, 4) a reduced number of mortality, and 5) achievement of better prognosis. However, the helmet use rate has gradually decreased recently. Therefore, we have to re-enforce the helmet use law, to modify the speed limit, and to reeducate the motorcyclists for safety driving behavior [5, 9, 15, 22].

Step 3: international collaborative program

TBI is a tough and complicated issue for developing countries. However, most of the developing countries can only afford a limited budget for prevention and treatment. As a result, these developing countries suffer from a lack of human resources and medical facilities. The most important and urgent thing for the developing countries is to cooperate with other developed countries to compensate for inadequate resources and to develop their own strategies and databases.

Kraus *et al.* reported in 1990 that the annual incidence rate of head injury was $132–430/10^5$, and the annual morality rate was $9–32/10^5$. Most of these data were collected from western countries. The developing countries, such as, Taiwan, Pakistan, India, Burkina Faso, Colombia, and Algeria, lack epidemiological data on TBI. After the year of 1990, developing countries gradually understood the fact that they faced the serious problem of TBI even more frequently than the western countries. From 1992 to 1995, comparative studies between developing countries (Taiwan, Algeria, Colombia, India, and Pakistan) and developed countries (Norway, Italy, USA, and Britain) were coordinated by the Global Spine and Head Injury Prevention Project (Global SHIP Project) [3, 10, 26, 27]. In 1997, a report on the incidence rates and morality rates of TBI in 5 developing countries and 4 developed countries appeared, as shown in Table 2. The comparative results can be used to develop and support their own injury prevention strategies for the developing countries [11, 25, 28, 30, 33].

Table 2. *Comparison of mortality rates and incidence rates related to TBI between developing countries and developed countries [28]*

	Incidence (/100,000)	Mortality (/100,000)	Year	Case fatality rate (%)
Developing countries				
Algeria, Blida	80	5	1989	–
Colombia, Cali	676	120	1990	–
India, Bangalore	150	–	1990	9.6
Pakistan, Multan	81	11	1990	–
Taiwan				
Taipei	182	19	1988–1992	10.6
Hualien	304	87	1988–1992	28.7
Developed countries				
Norway				
Trodelag	200	5.5	1984	2.8
Italy				
San Marino	468	–	1981–1982	–
USA				
San Diego	180	30	1984	6
Britain				
England	270	9	1981	–
Scotland	313	9	1981	–

Step 4: clinical research in moderate and severe TBI

In the past 5 years, several clinical trials were conducted in Taiwan and most of them were multi-center trials. All these trials focused on the acute stage, subacute stage, and long term monitoring of the TBI patients to reduce the severity and mortality rates and to improve their quality of life [8, 29].

After 1970, many researches showed that application of intensive care on severe TBI patients significantly decreased the severity and mortality rates. During the intensive care period, the most important strategies for the treatment of TBI were to reduce brain edema and prevent secondary insults to the ischemia brain. Based on the above concepts, we processed several trials as follows:

Our first trial showed that sedation with Propofol for severe and moderate TBI patients during the first 3–5 days of ICU stay effectively reduced intracranial pressure (ICP) and mortality rate, and maintained cerebral perfusion pressure (CPP) and the Glasgow Coma Scale (GCS) level. This trial also showed that ICP under 25 mmHg reduced the mortality rate to one fourth in comparison with those with ICP > 25 mmHg. The only major complication to avoid was the Propofol infusion syndrome. This complication is rare in clinical practice, but extremely dangerous once it has occurred [31].

However, another trial of hypertonic saline infusion, which was reported effective by some another in brain edema control, did not show much benefit for our TBI patients. The risk of complications induced by hypertonic saline, such as acute renal failure, was too high to be compensated by the benefits of the edema control.

In our recent ongoing trial, we have measured the brain tissue oxygenation level ($PbtO_2$) directly in 16 patients, and incorporated the data with ICP and CPP values. Our initial result showed that maintenance of adequate $PbtO_2$ by adjusting FiO_2 improved outcome in severe TBI patients.

For TBI patients in the subacute stage, we made a prospective trial for hyperbaric oxygen therapy (HBOT). We tried to apply HBOT concurrently with rehabilitation to TBI patients after stabilization of their condition, and HBOT improved the GCS level considerably in these subacute stage TBI patients. However, HBOT offered some benefits only for patients with GOS 4, but not for those with GOS 2 or 3. With concurrent therapy of rehabilitation, HBOT can provide some benefits for the subacute stage TBI patients (In submission).

In addition, we also used GOS, GOSE, and the Health-Related Quality of Life (HRQL) to follow up patients continuously. This will allow us to detect whether there were differences in prognosis and quality of life after the application of ICP monitoring and CPP treatment protocol. With the above experience, we further conducted another international collaborative study of Quality of Life after Brain Injury (QOLIBRI), which was coordinated by Prof. Jean-Luc TRUELLE. There were 23 institutes from 12 countries and regions joined in the project. With this trial we evaluated patients not only with GOS or GOSE, but also with overall health condition, feeling, emotion, action, human relationship, etc. These results could provide the long-term effectiveness for the application of ICP, CPP, $PbtO_2$, HBOT, etc.

Step 5: guidelines for management of severe TBI in Taiwan

The incidence of TBI in Taiwan has decreased gradually after implementing of the helmet use law. But the mortality rate of severe TBI still remains as high as 35%. The management principles of TBI have greatly changed in the past 20 years. In recent years, due to developments of new monitoring techniques, the management of severe TBI has been changed from mere lowering of IICP to prevention of brain ischemia, maintenance of CPP, and lowering of brain metabolism. The publications on TBI treatment principles have been updated rapidly, and therefore it is difficult to review all the articles with limited personnel.

Before and during meetings on severe TBI, we chose nine topics: ER Treatment, ICP monitoring, CPP fluid therapy, use of sedatives, nutrition, intracranial hypertension, seizure prophylaxis, second tier therapy and assigned each topic to one contributor. The contributors searched relevant information from 1966 to 2006 on Medicine database for English and Chinese articles. With their help, a guideline for management of severe TBI in Taiwan was eventually published in June 2007.

With this guideline, we can reeducate neurosurgeons and standardize the treatment procedures for moderate to severe TBI patients [7].

Summary

With our 26-year experience of severe TBI, stepwise approaches for prevention and treatment of TBI were implemented from 1991 to 2007. The project started from epidemiological studies of TBI, and then stepped into the multi-center trials and establishment of guide-

lines through intervention and international collaboration programs. The results from those approaches were significant with a drastic decline of TBI deaths. However, further studies including stem cell therapy, neurobehavioral studies, etc. are recommended.

Acknowledgements

The authors would like to acknowledge the grant (DOH-TD-B-111-002) from the Department of Health, Executive Yuan, Taiwan, the grant (NHRI-EX97-9707PI, NHRI-CN-HD9503S) from the National Health Research Institute, Taiwan, the grant (NSC 96-2314-B-038-010-MY2) from the National Science Council, Taiwan, and the grant (96001-62-010) from the Department of Health, Taipei, Taiwan.

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Acta Neurochir Suppl (2008) 101: 119–124

Printed in Austria

New approaches to increase statistical power in TBI trials: insights from the IMPACT study

A. I. R. Maas[1,2], H. F. Lingsma[2], on behalf of the IMPACT study group*

[1] Department of Neurosurgery, University Hospital Antwerp, Edegem, Belgium
[2] Center for Medical Decision Sciences, Department of Public Health, Erasmus MC, Rotterdam, The Netherlands

Summary

Introduction. None of the multi-centre phase III randomized controlled trials (RCTs) performed in TBI have convincingly demonstrated efficacy. Problems in clinical trial design and analysis may have contributed to these failures. Clinical trials in the TBI population pose several complicated methodological challenges, related especially to the heterogeneity of the population. In this paper we examine the issue of heterogeneity within the IMPACT (International Mission on Prognosis and Clinical Trial design in TBI) database and investigate the application of conventional and innovative methods for the statistical analysis of trials in TBI.

Methods and results. Simulation studies in the IMPACT database ($N = 9205$) showed substantial gains in efficiency with covariate adjustment. Adjusting for 7 important predictors yielded up to a 28% potential reduction in trial size. Ongoing analyses on the potential benefit of ordinal analysis, such as proportional odds and sliding dichotomy, gave promising results with even larger potential reductions in trial size.

Conclusion. The statistical power of RCTs in TBI can be considerably increased by applying covariate adjustment and by ordinal analysis methods of the GOS. These methods need to be considered for optimizing future TBI trials.

Keywords: Traumatic brain injury; trial design; prognosis; statistical models; glasgow outcome scale; mortality.

Introduction

Many randomized controlled trials (RCTs) have been performed to investigate the effectiveness of new therapies in traumatic brain injury (TBI), but none have convincingly shown benefit [14, 25]. Some agents investigated may have been truly ineffective, in some trials the pre-clinical work-up may have been insufficient, but others may have failed to show benefit due to shortcomings of the trial methodology. Clinical trials in TBI pose complex methodological challenges related to the heterogeneity of the disease.

TBI is not one single disease entity but includes a complex spectrum of pathologies and uncertainty exists as to whether pathophysiologic processes targeted are indeed active in individual patients and if so at what time after injury. Much basic and clinical research is needed before individualized mechanistic targeting can ever become clinically realistic.

Patients included in trials are heterogeneous in terms of clinical severity and baseline prognostic risk. It is here, that methodological approaches may be optimized to increase statistical power, by using the baseline prognostic risk of individual patients. This can be done both in the enrolment phase and in the statistical analysis.

Regarding the enrolment phase, sample size calculations are generally based on the assumption that every patient has a 50/50 chance of a good or poor outcome. When this ratio changes substantially, much greater sample sizes are required (Fig. 1). Previous studies have shown that approximately 40% of patients enrolled into a clinical trial in fact have an extreme prognosis [12]. Machado *et al.* found that sample sizes may be reduced by up to 30% if trials would be targeted to patients with an intermediate risk [17].

In this paper we examine the issue of heterogeneity within the IMPACT (International Mission on Prognosis and Clinical Trial design in TBI) database and investigate the application of conventional and innovative

* The IMPACT Study Group is a collaborative venture including the division of Community Health Sciences, University of Edinburgh Scotland, The Department of Neurosurgeru Virginia Commonwealth University, Richmond, USA, The Center for Medical Decision Sciences, Department of Public Health, Erasmus MC, Rotterdam, The Netherlands and University Hospital Antwerp, Belgium.

Correspondence: Andrew I. R. Maas, Department of Neurosurgery, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium. e-mails: Andrew.maas@uza.be, airmaas@erasmusmc.nl

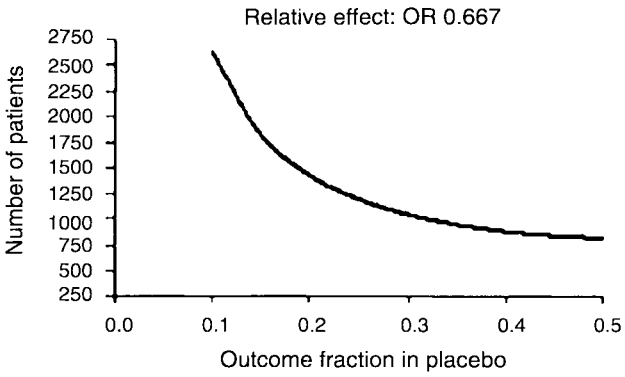

Fig. 1. Sample size calculation in relation to outcome fraction

methods for the statistical analysis of trials in TBI. The general aim of our studies is to optimize the design and analysis of clinical trials in TBI with the expectation of increasing the likelihood of demonstrating benefit of a truly effective new therapy or therapeutic agent in victims of a head injury.

Methods and results

Heterogeneity in the IMPACT database

The IMPACT (International Mission on Prognosis and Clinical Trial design in TBI) study was initially organized as a collaborative venture between the Erasmus University in Rotterdam, The Netherlands, the University of Edinburgh, Scotland, and the Virginia Commonwealth University Medical College in Richmond, Virginia, USA. Within this project we merged individual patient data from three observational studies and eight RCTs. This report focuses on results based on analyses of the studies currently included in the IMPACT database, but the work is ongoing, and we will be including more studies and refining analyses as the project continues. Details of the studies and data management of the IMPACT database have been described previously [18].

In Table 1 we describe relevant prognostic factors and outcome in the different studies in the IMPACT database. There is substantial heterogeneity in prognostic factors. For example, the median age varies between the studies from 26 to 38, the percentage of patients with a motor score 'no response' from 13 to 47% and the percentage of patients with two unresponsive pupils from 13 to 41%. There are also substantial differences between the studies in outcome distribution, e.g. the percentage of patients with an unfavorable outcome varies from 38 to 65%.

Outcome and Prognostic Models

The primary outcome measurement in all studies was the Glasgow Outcome Scale (GOS) at six months after injury. The GOS is an ordinal scale from 1 to 5 representing respectively dead, vegetative state, severe disability, moderate disability and good recovery.

To calculate baseline prognostic risk, extensive prognostic modeling was performed. This resulted in the development and validation of various prognostic models of increasing complexity [12]. A 'Core model' included age, motor score, and pupil reactivity; a '7-predictor model' additionally included information on secondary insults (hypoxia, hypotension), and CT characteristics (Marshall's CT classification; traumatic subarachnoid hemorrhage, tSAH) and a 'Full model' which included additional information on glucose and hemoglobin. Definitions of predictors were described in detail before [18].

Covariate Adjustment

To explore the influence of covariate adjustment on statistical power, extensive simulation studies were performed [10]. None of the RCTs included had demonstrated a significant treatment effect. We simulated a positive treatment effect that gave an unadjusted odds ratio (OR) of 0.57 (coefficient: –0.557, corresponding to an average absolute risk reduction of 10% in unfavorable outcome) [17]. Fifty percent of the patients were randomly allocated to the hypothesized treatment. Each regression model was applied in turn for this outcome to compare estimates of treatment effect. One thousand simulations were run using the original sample size for each study.

We calculated the reduction in sample size to express the gain in power for each of the adjusted models. The reduction in sample size is an attractive summary measure which is independent of the treatment effect and the original sample size [5]. The formula used was: $100 - 100 * [(\text{mean of Z score for reference model})/(\text{mean of Z score for adjusted model})]$ [2], where Z score is equal to the Wald statistic of the treatment effect coefficient [11]. Reduction in sample size calculations were performed in the Core model if we had information in all three variables, and in the 7-predictor model if we had at least five variables.

The reduction in sample size obtained with the regression models is illustrated in Fig. 2. Adjustment of the treatment effect for age, motor score and pupil reactivity (Core model) yielded a reduction in sample size between 16 and 23% in trials, and between 28 and 35% in surveys. Adjustment for the 7-predictor model yielded more reduction in sample size: between 20 and 28% in trials, and between 32 and 39% in surveys. Finally the full model lead to even larger potential reductions in sample size.

Ordinal analysis methods

In most trials the primary efficacy endpoint has been the GOS, dichotomized into unfavorable vs. favorable without relating the point of dichotomization to the initial prognostic risk. We consider that it may be better to exploit the ordinal nature of the GOS and to differentiate outcome analysis to the prognostic risk in individual patients. For these ordinal analysis methods of the GOS, two different approaches can be considered: proportional odds analysis, in which shifts in outcome are captured across the full range of the GOS and application of the sliding dichotomy, in which the point of dichotomy is differentiated according to baseline prognostic risk [20, 22].

In our ongoing work we perform simulation studies to explore the benefits of exploiting the ordinal nature of the GOS, either via the proportional odds model or with the sliding dichotomy. Also the incremental benefit of ordinal analysis methods when combined with covariate adjustment are studied. These benefits are again expressed as reduction in sample size.

Preliminary results indicate that there is clear potential for ordinal analysis of the GOS by proportional odds models or sliding dichotomy to further increase statistical power over and above the gains resulting from covariate adjustment.

Discussion

We illustrate the application of conventional and innovative methods for increasing statistical power in trials in TBI. We used the effects of covariate adjustment and explored the ordinal nature of the GOS. Previously we successfully developed and validated prognostic models to establish the baseline prognostic risk [3, 4, 12, 15, 19–21, 23, 24, 31]. Simulation studies showed that sub-

Table 1. *Distribution of prognostic factors and outcome across studies in the IMACT database*

	TINT $N=1118$	TIUS $N=1041$	Selfotel $N=409$	SAPHIR $N=919$	PEGSOD $N=1510$	HIT-I $N=350$	SKB $N=126$	HIT-II $N=819$	UK4 $N=812$	TCDB $N=604$	EBIC $N=822$
Age (median, 25^{th}–75^{th} p*)	30 (21–45)	30 (23–41)	28 (21–48)	32 (23–47)	27 (20–38)	34 (21–47)	27 (20–39)	33 (22–49)	36 (22–55)	26 (21–40)	38 (24–59)
Motor score (*n*, %*)											
No response/extension	141 (13)	152 (15)	55 (13)	264 (29)	655 (43)	163 (47)	56 (44)	280 (34)	200 (25)	243 (40)	230 (28)
Flexion abnormal	237 (21)	132 (13)	91 (22)	143 (16)	165 (11)	45 (13)	14 (11)	92 (11)	37 (5)	74 (12)	55 (7)
Flexion withdrawal	327 (29)	300 (29)	127 (31)	223 (24)	334 (22)	56 (16)	16 (13)	181 (22)	142 (17)	122 (20)	113 (14)
Localizes pain/obeys	413 (37)	457 (44)	136 (33)	286 (31)	356 (24)	77 (22)	23 (18)	207 (25)	232 (29)	134 (22)	281 (34)
Non testable	0 (0)	0 (0)	0 (0)	3 (3)	0 (0)	9 (3)	17 (13)	59 (7)	201 (25)	31 (5)	143 (17)
Pupillary reactivity (*n*, %*)				NA			NA				
Both responsive	831 (73)	709 (68)	316 (77)		779 (52)	235 (67)		583 (71)	445 (55)	300 (50)	527 (64)
One unresponsive	170 (15)	122 (12)	79 (19)		160 (11)	51 (15)		101 (12)	116 (14)	55 (9)	87 (11)
Both unresponsive	135 (12)	210 (20)	14 (3)		571 (38)	64 (18)		135 (16)	251 (31)	249 (41)	208 (25)
CT classification (*n*, %*)					NA	NA			NA	NA	
I	51 (5)	99 (10)	2 (1)	39 (4)			3 (2)	69 (9)			101 (12)
II	424 (38)	360 (35)	152 (37)	358 (39)			52 (40)	270 (33)			229 (28)
III	218 (20)	196 (19)	94 (23)	145 (16)			40 (32)	89 (11)			84 (10)
IV	46 (4)	39 (4)	26 (6)	22 (3)			2 (2)	31 (4)			21 (3)
V	289 (26)	232 (23)	108 (26)	283 (31)			0 (0)	314 (39)			213 (26)
VI	81 (7)	103 (10)	27 (7)	61 (7)			30 (24)	36 (4)			171 (21)
tSAH (*n*, %*)	567 (52)	420 (43)	317 (78)	399 (44)	619 (41)	71 (28)	99 (79)	268 (33)	NA	227 (43)	331 (45)
Hypoxia (*n*, %*)	149 (15)	266 (29)	24 (6)	110 (13)	NA	NA	29 (35)	NA	227 (24)	109 (18)	236 (28)
Hypotension (*n*, %*)	155 (14)	224 (22)	NA	128 (15)	NA	17 (5)	21 (20)	81 (10)	241 (25)	143 (24)	201 (24)
Glucose, mmol/L (median, 25^{th}–75^{th} p*)	7.8 (6.4–10.2)	8.5 (6.9–10.6)	NA	7.1 (5.9–8.7)	8.9 (7.3–11.2)	8.3 (6.7–9.7)	9.1 (7.2–10.8)	NA	NA	NA	NA
Hb, g/dL (median, 25^{th}–75^{th} p*)	12.5 (9.9–14)	13.3 (11.7–14.7)	NA	11.4 (10.2–12.9)	13.5 (11.8–14.7)	13.5 (12.0–14.7)	12.3 (10.4–13.8)	NA	NA	NA	NA
Unfavorable outcome (*n*, %*)	456 (41)	395 (38)	177 (43)	378 (41)	774 (51)	171 (49)	70 (56)	328 (40)	518 (64)	393 (65)	422 (51)

* All percentages are percentage of number available.
NA Not available.

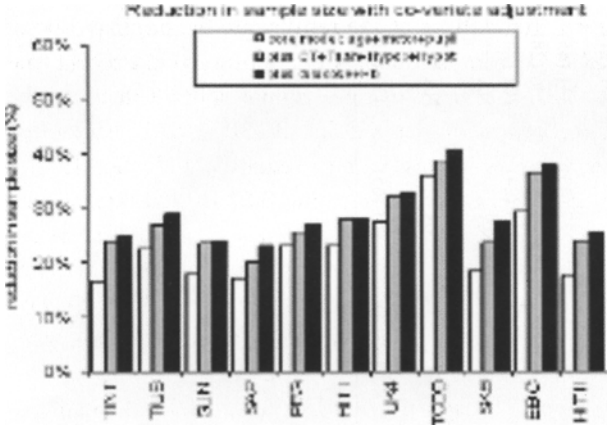

Fig. 2. Simulation studies showing reduction in sample size with covariate adjustment

tantial gains in efficiency could be obtained with covariate adjustment and ordinal analysis methods of the GOS.

Heterogeneity and the enrolment phase

Different approaches for dealing with the heterogeneity of TBI populations in the enrolment phase have been suggested. Machado *et al.* used data from the EBIC survey, and defined models on different TBI prognostic groups, based on three predictors [17]. They quantified the power that could be achieved when the analysis was targeted to some prognostic groups (e.g. defined by clinical or radiological characteristics), and when different treatment effects were defined for different prognostic groups (e.g. treatment benefit only in patients with intermediate prognosis). For instance, for a moderate/severe TBI population and with a uniform treatment effect, a trial with 344 patients with intermediate prognosis per arm had the same 90% power as a trial with 500 unselected patients per arm – that is, the sample size could be reduced by 31% with no decrease in the power. The disadvantage of prognostic targeting, however, is that recruitment is substantially reduced, and we feel that this approach has been largely overtaken by our work for dealing with heterogeneity in the statistical analysis.

Covariate adjustment

In simulation studies we found that the use of more complex models yielded greater reductions in sample size with covariate adjustment. A larger reduction in sample size was observed when the 7-predictor model was used in comparison to the Core model with 3 predictors. We do however not propose to actually reduce sample size, but our methods lead to an increase in power to detect small but clinically relevant treatment effects.

Reductions in sample size of approximately 20% with the Core model and around 24% with the 7-predictor model in TBI trials are greater than those obtained in trials of other fields in medicine. For instance, adjustment for 17 predictors of 30-day mortality in patients with acute myocardial infarction included in the GUSTO-I trial reduced the sample size requirements by only 15% [29]. This probably reflects the greater heterogeneity of TBI populations.

Ordinal analysis methods

Our preliminary results indicate that substantial increases in statistical power of TBI trials may be obtained by exploiting the ordinal nature of the GOS. These findings are supported by recently published, related work which is being conducted in the context of stroke outcome scales [26]. The GOS has been criticized for being insensitive. This insensitivity is further increased by the accepted practice of dichotomizing the GOS to produce two groups: favorable outcome (moderate disability, good recovery) and unfavorable outcome (dead, vegetative, severe disability). Exploiting the ordinal nature of the GOS is attractive both from a statistical and a clinical perspective.

From a statistical perspective, optimal statistical power is to be present when the point of dichotomization results in a 50:50 distribution of outcome categories, and this is better achieved when differentiating the point of dichotomization according to baseline prognostic risk. The applicability of such a "sliding dichotomy", as first proposed for analysis in stroke studies, has hitherto been insufficiently investigated in the field of TBI [1, 22]. From a clinical perspective, it may be argued that the common practice of defining clinical benefit as the requirement for a substantial number of treated patients to cross a prespecified, fixed and artificially determined boundary (the point of dichotomization) makes little sense in respect to the heterogeneity of the population.

It should be recognized, however, that the traditional favorable/unfavorable dichotomy has become established in part through a value judgment that the goal in managing TBI is to help the patient achieve a 'favorable' outcome. The appropriate definition of what a favorable outcome in a patient may be, given the initial severity of injury and pre-morbid situation remains a point of ethical debate.

Future challenges

Within the continuing IMPACT study, we will further expand and refine on the preliminary results presented here for dealing with the complex heterogeneity of the patient population in terms of injury severity and baseline prognostic risk. Other challenges remain and will be addressed.

Heterogeneity in patient management may also be relevant. In fact, a new therapy under investigation represents no more than an element superimposed upon a wide variation of treatment approaches deployed in individual centers. Center effects are generally viewed as unexplained variations in outcome for apparently similar patients treated in different centers. This often relates to caseload with a considerable body of general medical literature documenting volume/outcome effects. Benefits of concentration of care have been demonstrated in spontaneous subarachnoid haemorrhage and intracerebral haemorrhage [2, 8]. The impact of centre effects within a clinical trial of TBI has seldom been studied. Clifton *et al.* reported considerable inter-centre variability within the NABIS hypothermia study [6]. Significant differences in mortality were found between high and low enrolling centers in the most recent trial in TBI, investigating the efficacy of dexanabinol [16]. The wide variability in choice and sequence of basic therapeutic approaches between centers is a reflection of the uncertainties in many aspects of basic management. A wide variability in choice and sequence of basic therapeutic approaches exists between centers, even within RCTs [13]. Two different approaches may be pursued: One is to minimize variability by restrictive enrolment criteria and rigorous standardization of treatment, and the other is to recruit so many patients in a 'mega trial', that variability can be ignored. An example of the latter approach is the CRASH study [9, 27]. The relative merits of these two contrasting approaches need to be determined.

Accurate and consistent outcome determination is a prerequisite for the success of any clinical study or trial in TBI [33]. The 8-point extended GOS (GOSE) has been introduced to increase sensitivity of outcome assessment and the use of a structured interview is advocated to obtain more consistency in outcome assignment [32]. Currently there is insufficient knowledge on how the introduction of the GOSE may have changed the outcome distribution. In TBI, the outcome distribution of the 5-point GOS is U-shaped but a recent study on prehospital administration of hypertonic saline utilizing the 8-point GOSE does not show this U-shaped distribution even after collapsing the results into the original 5-point GOS [7]. Similar findings were observed in a recent trial in TBI, the Pharmos dexanabinol study. Effects of the introduction of the 8-point GOSE and the structured interview for its assessment require clarification [33].

By definition outcome after TBI is multidimensional and we realize that the GOS is only a global measure. Various trials in TBI have included different measures for outcome (Barthel, neuropsychological tests, Quality of Life) but only one has attempted to combine these into a multi factorial scale [30].

In many fields of medicine Health Related Quality of Life (HRQoL) measurements are considered at least as relevant as outcome determined by professionals, but relatively few studies in TBI have utilized HRQoL measures. Quality of Life scales include generic scales such as the SF36, WHOQoL, EuroQol and the Community Integration Questionnaire, and disease-specific scales. Few disease-specific scales exist for TBI. Recently a new disease-specific scale for QoL assessment in TBI has been developed and is currently being validated: the QoLiBRI (Quality of Life in Brain Injury) [28]. Ultimately we hope to provide evidence-based recommendations for optimizing the design and analysis of future TBI trials, minimising the chance of erroneously discarding effective new treatment modalities. The results presented here illustrate the potential of some approaches for more powerful statistical analysis.

Acknowledgements

The authors acknowledge collaboration with the American and European Brain Injury Consortia. Grant support was provided by NIH NS 42691.

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Acta Neurochir Suppl (2008) 101: 125–129

Printed in Austria

The QOLIBRI- towards a quality of life tool after traumatic brain injury: current developments in Asia

J. L. Truelle, K. von Wild, S. Höfer, E. Neugebauer, T. Lischetzke, N. von Steinbüchel, and the QOLIBRI Group*

Service de médecine physique et de réadaptation Centre hospitalo-universitaire, Garches, France

Summary

Introduction. There is no disease-specific health-related quality of life (HRQoL) tool devoted to traumatic brain injury (TBI).

Material and methods. Over 1500 TBI patients from 10 countries filled out a preliminary version of the QOLIBRI taking TBI specificities into account. 3 successive versions and consecutive statistical analyses were necessary to get a psychometrically-reliable tool.

Results. The QOLIBRI final version, filled out in 15 min, consists of 2 parts. The first part assesses satisfaction with HRQoL and is composed of 6 overall items and 29 items allocated to 4 subscales: thinking, feelings, autonomy and social aspects. The second part, devoted to "bothered" questions, is composed of 12 items in 2 subscales: negative feelings and restrictions. The 6 subscales meet standard psychometric criteria. In addition, 2 items evaluate medical-oriented aspects. The questionnaire is validated in German, Finnish, Italian, French, English, Dutch.

Conclusion. TBI patients may now be assessed, beyond more "objective" measures including handicap and recovery, with a new measure of assessing the TBI patient's own opinion on his/her HRQoL, applicable across different populations and cultures. Validations in China Mainland, Hong-Kong, Taiwan, Japan, Egypt, Poland, Norway, Indonesia, and Malaya are on the way.

Keywords: Traumatic brain injury; head injury outcome; health-related quality of life; disease-specific assessment.

Introduction

Some HRQoL instruments enhance the assessment of psychological well-being more than others. Moreover, a trend can be observed over the different fields of application to complement generic tools such as SF-36 [5, 6] with specific ones, taking into account the characteristics of one population, disease or condition [4].

Traumatic brain injury (TBI) can have devastating consequences for the lives of the persons in question resulting in enormous human and economic aspects. In addition, TBI leads to a specific handicap, often hidden, related to a combination of rather limited physical sequelae but also cognitive and – moreover – behavioural troubles. And 3/4 of the TBI are less than 30 years old. Nevertheless, until now, there has not been a TBI-specific HRQoL tool in use.

The development of specific HRQoL instruments for multiple trauma, spinal cord injury and TBI was the objective of the conference on QOL after multiple trauma held in Wermelskirchen (D) in October 1999 [1].

The participants of the TBI subgroup decided to create a clinical research group under the aegis of 3 societies: EMN (Euroacademia Multidisciplinaria Neurotraumatologica), EBIS (European Brain Injury Society) and NBIRTT (National Brain Injury Research, Treatment and Training foundation in the US).

As of today, the group includes representatives from 23 countries: Argentina, Australia, Belgium, China,

*The QOLIBRI group is composed of a Steering Committee: M. Bullinger (D), A. Maas (B), E. Neugebauer (D), J. Powell (UK), N. von Steinbüchel (D), K. von Wild (D), G. Zitnay (USA) directed by J. L. Truelle (F), Chairman: N. von Steinbüchel (D).

Data acquisition is carried out by country coordinators: A. Basso (ARG), C. Croisiaux (B), L. Braga (BR), Z. Thong (CH Mainland), N. von Steinbüchel and N. Sasse (D), A. L. Christensen (DK), A. Etribi (EG), J. Sarajuuri and S. Koskinen (FN), J. L. Truelle (F), E. Tazopoulou (GR), W. S. Poon (HK), R. Formisano (I), Y. Katayama (JP), A. Maas and W. Bakx (NL), M. Pachalska (PO), J. Leon-Carrion (SP), B. L. Lichterman (RU), W. T. Chiu (TW), J. Powell (UK), J. DaVanzo (USA) and G. Hawthrone (AUS).

NB: This text refers to our 2-day workshop with Asian partners and our oral communications at the 5th Scientific Meeting of the Committee of Neurorehabilitation and Reconstructive Neurosurgery, World Federation of Neurosurgical Societies, Chairman Y. Takayama (Japan), held in Taipei, on September 12–16, 2007.

Correspondence: Jean-Luc Truelle, MD, Service de Médecine Physique et de Réadaptation Centre Hospitalo-Universitaire, 104, Boulevard Raymond-Poincaré F, 92380 Garches, France.
e-mail: jean-luc.truelle@wanadoo.fr

Fig. 1. Workshop of the TBI-QOL group at the "Office National de la Chasse", Rambouillet during the 5th EMN-EBIS Congress on traumatic brain injury in Paris September 20–23, 2000. From *left* to *right*: Richard Greenwood (London, UK) and assistant, Pierre North (Mulhouse F), Michèle Montreuil (Paris F), Jean-Luc Truelle, Chairman (Paris-Suresnes F), Klaus von Wild (Muenster D), Eddy Neugebauer (Cologne D), Anne-Lise Christensen (Copenhaegen DK), Matej Lipovsek (Maribor, Slovenia), Hans-Erich Diemath (Salzburg AT), Philippe Azouvi (Paris-Garches F)

Taiwan, Hong Kong, Denmark, Egypt, Finland, France, Germany, Indonesia, Italy, Japan, Jordan, Malaya, Norway, Poland, Romania, Russia, The Netherlands, Sweden, United Kingdom, The USA. The objective of the group was to develop a TBI-specific QOL tool [12].

Materials and methods

The population was defined as follows: TBI patients from age 17 to 68, Glasgow Outcome Scale Extended [13] superior or equal to 3, from 3 months to 18 years after injury, able to understand, answer and cooperate, without spinal cord injury, ongoing psychiatric disease or addiction, or terminal illness.

The first steps of development were primarily based on a literature review and on an international expert consensus, initiated in 1999, during a conference held in Wermelskirchen [1]. From the literature, we selected four tools considered as the most contributive instruments to the HRQoL concept and to its applicability for persons after TBI: EBIQ (European Brain Injury Questionnaire), a TBI specific subjective rehabilitation questionnaire [3]; BICRO-39, a handicap tool devoted to brain injury [14]; SQLP (Subjective Quality of Life Profile), a generic QOL tool, which has been applied to TBI [7] ; QOLBI (Quality of Life after Brain Injury), a TBI- specific QOL questionnaire [11].

Then, according to expert consensus, 56 items out of 160 were selected and worded, following the key- question: "How satisfied are you with...?"(for example your ability to concentrate). The respondent has to answer *via* a 5-point Lickert scale: not at all satisfied, slightly, moderately, quite, very satisfied.

The 56 items were divided into 6 domains: physical, cognitive, psychological, functional, social, current situation and future prospects.

Furthermore, symptoms were assessed with a second key-question: "How bothered are you by ...". This reflects how difficult it is to use the key-question "How satisfied are you..." for example, "with your epileptic seizures or your loneliness"! Therefore, it was decided to create a second part within the tool, putting together those types of questions under the key-question: "How bothered are you with...?"

Fig. 2. Senior authors Prof. J. -L. Truelle and Prof. N. von Steinbüchel responsible for the elaboration of the QOLIBRI assessment tool and publication

In 2005, that TBI-specific HRQoL tool was called "QOLIBRI" (Quality of Life after Traumatic Brain Injury).

The international validation process [10] was driven by N. Von Steinbüchel, head of the methodological centre together with M. Bullinger, T. Lischetzke and S. Höfer. The validation file comprised:

- for the patient: informed consent; QOLIBRI self-rated questionnaire (without support for persons with mild and moderate handicap, with examiner's help for severely disabled); SF-36, a HRQoL generic scale considered as a universal reference and already applied to TBI [4]; HADS to evaluate depression and anxiety; co-morbidity, health status and sociodemography questionnaires.
- for the examiner: Glasgow Outcome Scale Extended (GOSE) as a TBI-specific handicap scale [13]; clinical state including Glasgow Coma Score; MMSE or TICS to evaluate the ability to understand and to answer; PCRS-anosognosia scale, selected in a few centres.
- for the relative's proxy: PCRS, SF-36 and QOLIBRI (in selected centres).

Regarding the translations, each language representative had to recruit 2 native speakers, both TBI specialists and fluent in English in order to perform 2 forward translations from English into their native language. Secondly, the language representative recruited one English native speaker, fluent as well in the language to be translated, who performed the backward translation into English. The third step consisted of achieving a harmonised translation in the target language, taking into account the 3 versions (2 forward and 1 backward).

The next step consisted of testing the harmonised translation with 5 healthy persons together with 5 persons after TBI.

This cognitive debriefing procedure allows to identify conceptual problems, compare the different language versions and improve the wording, when necessary. Translation processes and cognitive debriefing are checked by the methodologists.

For the validation of each language version, 150–200 patients were assessed, involving 3–5 different teams per country. Each team was requested to recruit a minimum of 25 patients. The testing was mostly performed by neuropsychologists. Finally, the data were transfered, via SPSS, to the methodological centre. Statistical analyses identified sample characteristics, feasibility, descriptive psychometric properties on item and scale level (factorial validity, convergent and discriminative validity, etc.).

Preliminary results

Today, the QOLIBRI has been translated into 14 languages: Chinese (Mandarin and Cantonese), Danish, Dutch, English, Finnish, French, German, Italian, Japanese, Polish, Spanish, Norwegian and Malayan. The validation process went through 3 successive statistical analyses and consecutive reformulations of some QOLIBRI-items including a reduction of the item number to 49.

More than 1500 persons after TBI took part in this process. The QOLIBRI final version comprises 2 parts. The first assessing satisfaction with some HRQoL-aspects is composed of 6 overall items and 29 items in 4 subscales: thinking, feelings, autonomy, social aspects. The second part devoted to "bothered" items is composed of 12 items in 2 subscales: negative feelings and restrictions. 2 additional items were added. The 6 subscales meet standard psychometric criteria. The final version was first validated in German, Finnish, Italian, French, English and Dutch. The average time to fill out the QOLIBRI requires 15–20 min.

The QOLIBRI was administered through self-report in 83.1%, *via* interview in 16.3% of the population. The population tested with the last version (675 patients) has a sex ratio (male/female) of 71.1 %, a mean age of 40.2, a mean GCS of 8.7. The length of time after injury is 5.7 years, the GOSE distributed in 3:2.5%; 4:9.7; 5:33.5; 6:22.0; 7:14.4; 8:7.4. The descriptive psychometric results are satisfactory. The Cronbach's alpha is superior or equal to 0.84 for the 5 satisfaction subscales and 1 bothered scale (negative feelings). There are few correlations between individual QOLIBRI items and GCS or time since injury. Co-morbidity, GOSE, HADS are highly correlated with QOLIBRI items. Expected correlations between SF-36 and QOLIBRI are found. QOLIBRI clearly demonstrates an added value as compared to SF-36, especially for psychosocial and emotional HRQoL dimensions.

Discussion

In 2005, more than 400 English-speaking papers devoted to TBI and QOL were found in the literature regarding the topics HRQoL and TBI [8, 9]. However, there is no validated TBI-specific HRQoL instrument yet. The statistical analyses from 3 consecutive validation studies demonstrate the psychometric quality of the QOLIBRI. As mentioned before there are, as of today, 6 validated versions of the QOLIBRI; many more are being processed. Three years of international experience of the use of QOLIBRI show both the need and interest for this disease-specific HRQoL instrument: namely to add, to more "objective" outcome assessments for the lesions, deficiencies, incapacities, handicap, a subjective evaluation which reflects the opinion of the patient himself/herself about his/her HRQoL. Indeed, our patient's satisfaction is our ultimate objective. Therefore, asking his/her subjective opinion on his/her HRQoL can not be avoided.

Secondly, there are few diseases, if any, where the family role is so essential. In addition, Germany, France and Italy also developed QOLIBRI versions for proxies. Therefore relative's proxy contribution in evaluating a possible discrepancy between patient's view of his/her HRQoL and the level of satisfaction of the relative regarding the patient's situation is assessed [7, 11]. Especially the involvement of the family in a therapeutic program is crucial and can be supported by such an assessment. QOLIBRI is user-friendly: more than 4 out of 5 of the TBI adults are able to fill out the questionnaire without any help, in about 15 min, thus sparing the examiner's time.

Fig. 3. QOLIBRI representatives during the harmonization workshop for Chinese and Japanese interpretations: Taipei Medical College September 12, 2007, on the occasion of 5th Conference of the Committee of Neurorehabilitation and Reconstructive Neurosurgery of the World Federation of Neurosurgical Societies (WFNS) in conjunction with the 2nd Congress of the International Society of Reconstructive Neurosurgery (ISRN). From *left* to *right*: Prof. Mou-Roung Lin (Taipei Medical University) Dr. Stephanie NG (id) Prof. Wai Sang Poon, Director of the Neurosurgical Department Prince of Wales Hospital (Hong Kong China), Prof. Wen-Ta Chiu, AMN President, Congress President of ISRN (Taipei Medical University), Prof. Nicole von Steinbüchel, head of the QOLIBRI methodological centre (University of Göttingen, Germany), Prof. Jean-Luc Truelle, Chairman of the QOLIBRI Task Force (University Hospital of Garches, France), Prof. Klaus von Wild (Muenster, Germany), Honorary President EMN, Founding and Honorary Chairman WFNS Neurorehabilitation Committee, Dr. Takeshi Maeda, neurological surgery (Nihon University, Japan)

The involvement of Asian countries

The main objective now is to design and validate new versions. This was also the main aim of our 2 workshops and oral communications in the 5th Scientific Meeting of the WFNS (World Federation of Neurosurgical Societies) Neurorehabilitation Committee held in Taipei, on September 2007. The link between Western and Asian countries was established thanks to Prof. Klaus von Wild as well as the strong interest of Prof. Wen-Ta Chiu and of our Asian partners. For 2 days, N. von Steinbüchel (D), J. L. Truelle (F), K. von Wild (D) and E. Neugebauer (D) presented the QOLIBRI process and met R. Chiang, W. T. Chiu, K. S. Hung, S. HD, S. J. Huang, C. Liha, M. R. Lin, S. J. Lee, C. C. Lin, J. Zhang and colleagues (Taiwan), W. S. Poon (Hong-Kong), Y. Katayama, K. Uemura, T. Maeda (Japan) to perform the first steps towards language harmonisation.

This work helped to improve the item wording, generally moving from literal translation to more pertinent and meaningful wording for the patient, taking into account the culture of various Asian countries (China Mainland -Tianjin and Beijing-, Hong Kong, Taiwan, Japan). For instance, negative formulations were avoided in the translations dedicated to these countries. Therefore, the so-called "bothered" part of the QOLIBRI was not as acceptable and required significant reformulations. For a few items, it appeared necessary to divide the question into 2 sentences, the first one being general, conceptual and not intrusive, the second one more targeted and specific.

As it was foreseeable, the comparison between English and Asian formulations was strongly facilitated by the participants who had good knowledge of English, of the HRQoL concept and of TBI care in Asia and Europe. We identified some differences between Mandarin and Cantonese Chinese. Differences were not as strong between Hong-Kong and Taiwan Chinese.

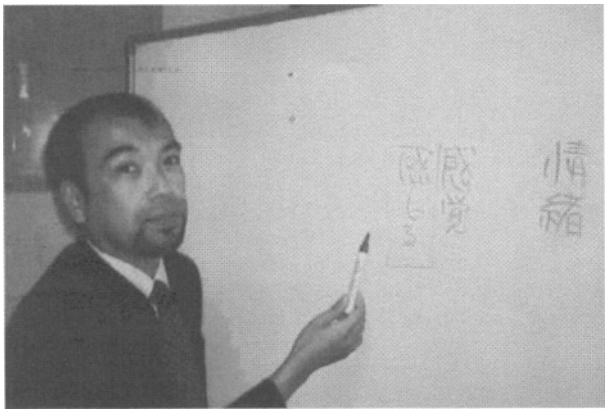

Fig. 4. Dr. T. Maeda, Department of Neurological Surgery Nihon University School of Medicine, Tokyo, Japan, explaining similarities and differences between Mandarin Chinese and Japanese languages for appropriate interpretation of the QOLIBRI questionnaire

Finally, this friendly, very informative and open exchange does support a clear interest for cross-cultural HRQoL studies [2] in persons after TBI, which are foreseen as one of the main objectives of QOLIBRI's further development. In conclusion, this specific HRQoL tool for persons after TBI intends to reflect a metadimension, beyond the handicap, in TBI outcome measures, taking into account the unavoidable and subjective point of view of the person in question. It allows to achieve the assessment of each individual's progress, the efficency of a therapeutic programme and to re-prioritise the goals of rehabilitation, taking into account the patient's and family's needs. Moreover, this self-rated questionnaire (15 min long) can work as a fast screening of troubles, needs, strengths and resources of persons who have suffered a TBI.

Aknowledgements

This paper was achieved under the auspices of the QOLIBRI international research group chaired by Prof. J. L. Truelle. This group was formed under the aegis of 3 societies: EMN, EBIS and NBIRTT, with grants from NBIRTT, Les Gueules Cassées, Fondation MAAF Assurances, France Traumatisme Crânien, CEREB-Protect, Medical Faculties of the Universities of Geneva and Göttingen. Copyright of photographs by K. von Wild.

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Acta Neurochir Suppl (2008) 101: 131–136

Printed in Austria

Evaluation of optimal cerebral perfusion pressure in severe traumatic brain injury

J. W. Lin[1,2], J. T. Tsai[3,4], C. M. Lin[1,2], L. M. Lee[5,6], K. S. Hung[1], S. J. Huang[7], S. H. Hsiao[8], W. Y. Chung[9], M. D. Tsai[10], C. C. Hsia[11], C. C. Hung[12], W. T. Chiu[1,6]

[1] Department of Neurosurgery, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan
[2] Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[3] Institute of Biomedical Engineering, National Yang-Ming University, Taipei, Taiwan
[4] Department of Radiation-oncology, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan
[5] Department of Urology, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan
[6] Graduate Institute of Injury Prevention and Control, Taipei Medical University, Taipei, Taiwan
[7] Department of Neurosurgery, National Taiwan University Hospital, Taipei, Taiwan
[8] Department of Neurosurgery, Taipei City Hospital-Renai Branch, Taipei, Taiwan
[9] Department of Neurosurgery, Taipei Veterans General Hospital, Taipei, Taiwan
[10] Department of Neurosurgery, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan
[11] Department of Neurosurgery, Tri-Service General Hospital, Taipei, Taiwan
[12] Department of Neurosurgery, Taipei Medical University Hospital, Taipei, Taiwan

Summary

Traumatic brain injury (TBI) is a major cause of death and disability. In the 2000 guidelines, one of the suggestions for TBI treatment was to maintain cerebral perfusion pressure (CPP) ≤ 70 mmHg. But in the 2003 guidelines, the suggestion was changed to ≤ 60 mmHg. There have been some discrepancies of opinions about this recommendation in recent publications.

In this study, we retrospectively reviewed 305 severe TBI (STBI) patients with Glasgow Coma Scales (GCS) ≤ 8 between January 1, 2002 and March 31, 2003. The study group was stratified according to use or nonuse of intracranial pressure (ICP) monitoring, ICP levels, ages, and GCS levels in order to test the correlation between CCP and the prognosis.

The patients <50-year-old, with higher GCS level, with ICP monitoring, and with ICP levels <20 mmHg had lower mortality rates and better prognosis (GOS) ($p < 0.05$ or 0.001). The patients in the GCS 3–5 subgroup had a significantly lower mortality and better prognosis if the CPP value was maintained higher than 70 mmHg ($p < 0.05$)

The optimal CPP maintained ≤ 60 mmHg did not fit in all STBI patients. Our study concludes that it is critical to maintain CPP substantially higher in lower GCS level patients.

Keywords: Traumatic brain injury (TBI); cerebral perfusion pressure (CPP); intracranial pressure (ICP); Glasgow coma scale (GCS); Glasgow outcome scale (GOS).

Correspondence: Wen-Ta Chiu, Department of Neurosurgery, Taipei Medical University-Wan-Fang Medical Center, Taiwan, Graduate Institute of Injury Prevention and Control, 111, Section 3, Hsing-Long Road, Taipei, Taiwan. e-mail: wtchiu@tmu.edu.tw

Introduction

Traumatic brain injury (TBI) is a major cause of death and disability. In the United States, 1.5 million people have head trauma every year and 1.1 million people are treated in emergency [14]. Among them, 235,000 persons are hospitalized for TBI, 50,000 patients die, and 90,000 patients are disabled [5, 11, 12]. The Brain Trauma Foundation Neurological Surgeons and American Association, according to Evidence-Based Medicine, developed guidelines for managing patients with severe TBI (STBI) in 1995 [10]. Treating patients with guidelines can indeed reduce mortality. The 2000 guidelines of cerebral perfusion pressure-oriented treatment for TBI suggested that the adequate cerebral perfusion pressure (CPP) must be higher than 70 mmHg [7]. But in 2003, the concept was changed: It was also suggested that that the maintenance of CPP at more than 60 mmHg was now considered adequate to prevent brain ischemic damage [15]. It was also suggested that the changes would reduce complications (such as acute respiratory distress syndrome (ARDS) [4]) related to the excessive use of fluid and inotropic drugs for maintaining cerebral perfusion pressure. In recent articles, there was still some argument against this drastic change, especially in how to achieve an

optimal cerebral perfusion pressure to prevent brain ischemia and how to avoid complications [4, 6, 12]. The main purpose of this study was to seek the optimal CPP for STBI patients with special characteristics and prognosis.

Materials and methods

In this study, we retrospectively reviewed 305 patients from eight medical centers in Taiwan between January 1, 2002 and March 31, 2003. Eligible candidates were those in-patients with STBI (initial Glasgow Coma Scale (GCS) ≤ 8). Medical records were collected and analyzed. The exclusion criteria included (1) death on arrival, (2) complete recovery within 24 h of admission without neurological deficits, (3) drunkenness, and (4) coma due to severe traumatic injury but without any definite lesion found in brain CT scans.

The patients were divided into two groups. Based on STBI guidelines, the study group patients were treated with the application of intracranial pressure (ICP) monitoring for adjusting ICP and CPP. The control group patients were treated mainly by conventional lowering of ICP (such as hyperventilation, head-up position, and empirical use of the osmotic diuretics) without ICP monitoring. We stratified the study group by (1) ICP, (2) age, and (3) GCS 6 h within admission to correlate the relationships between CPP and prognosis among these subgroups. We recorded age, diagnosis, GCS, use of ICP monitoring, ICP level, CPP, partial pressure of carbon dioxide in arterial blood ($PaCO_2$), use of vasopressors, and use of sedations during the intensive care period for further analysis.

For the outcome, we evaluated the prognosis at the time of discharge and on the third month after trauma. All the outcomes were scored with the Glasgow Outcome Scale (GOS). The score were then stratified into two major categories, namely, death (GOS 1) vs. survival (GOS 2–5) and poor outcome (GOS 1–3) vs. good outcome (GOS 4–5). The prognosis between the study group and control group were analyzed with variables of ICP, ages, CPP, and GCS.

The whole statistical analysis was performed with SPSS 11.0. We analyzed the basic information on patients with descriptive statistics and compared the variables and GOS between both groups with the Chi-square test. The differences between the groups were considered significant if p-values were less than 0.05.

Results

Among these 305 patients, 283 patients had complete data available for analysis. The male-to-female sex ratio was 3:1. Some factors were correlated with mortality before the discharge of patients and at 3 months follow-up (Table 1). The analyzed factors included age, GCS level, ICP monitoring or not, ICP level, and the CPP value during the period of intensive care. All the p-values were <0.05 or 0.001. The patients younger than 50 Y/O appeared to have a better chance to survive ($p<0.05$). The more severe the GCS, the higher the mortality rate was. Incorporation of the ICP monitoring effectively reduced the mortality ($p<0.001$). If the ICP level was ever raised up over 20 mmHg during the intensive care, the patients had

Table 1. *Factors influencing the patient mortality rate*

	Mortality before discharge			Mortality in 3 months F/U		
	Death	Survive	p-value	Death	Survive	p-value
Age						
<50 Y/O	70 (43.5%)	91 (56.5%)	0.040	70 (44.6%)	87 (55.4%)	0.025
≥50 Y/O	66 (55.9%)	52 (44.1%)		66 (58.4%)	47 (41.6%)	
GCS						
3	69 (81.2%)	16 (18.8%)	<0.001	69 (84.1%)	13 (15.9%)	<0.001
4	26 (70.3%)	11 (29.7%)		26 (72.2%)	10 (27.8%)	
5	9 (45.0%)	11 (55.0%)		9 (45.0%)	11 (55.0%)	
6	17 (34.7%)	32 (65.3%)		17 (37.0%)	29 (63.0%)	
7	10 (23.8%)	32 (76.2%)		10 (24.4%)	31 (75.6%)	
8	3 (9.7%)	28 (90.3%)		3 (9.7%)	28 (90.3%)	
ICP monitoring						
Yes	38 (33.9%)	74 (66.1%)	<0.001	38 (34.5%)	72 (65.5%)	<0.001
No	102 (59.3%)	70 (40.7%)		102 (61.8%)	63 (38.2%)	
ICP						
<20 mmHg	14 (19.2%)	59 (80.8%)	<0.001	14 (20.0%)	56 (80.0%)	<0.001
≥20 mmHg	23 (53.5%)	20 (46.5%)		23 (53.5%)	20 (46.5%)	
CPP						
<60 mmHg	13 (76.5%)	4 (23.5%)	<0.001	13 (76.5%)	4 (23.5%)	<0.001
≥60 mmHg	12 (14.5%)	71 (85.5%)		12 (14.5%)	71 (85.5%)	
<70 mmHg	17 (43.6%)	22 (56.4%)	<0.001	17 (43.6%)	22 (56.4%)	<0.001
≥70 mmHg	8 (13.1%)	53 (86.9%)		8 (13.1%)	53 (86.9%)	

High lighted data were the p-values without significant difference.
Mortality: GOS 1.
Survival: GOS 2–5.

Table 2. *Factors influencing the patient outcome and prognosis*

	Outcome before discharge			3 months F/U outcome		
	Poor	Good	*p*-value	Poor	Good	*p*-value
Age						
<50 Y/O	115 (71.4%)	46 (28.6%)	0.035	104 (66.2%)	53 (33.8%)	0.014
≥50 Y/O	97 (82.2%)	21 (17.8%)		90 (79.6%)	23 (20.4%)	
GCS						
3	84 (98.8%)	1 (1.2%)	<0.001	81 (98.8%)	1 (1.2%)	<0.001
4	34 (91.9%)	3 (8.1%)		33 (91.7%)	3 (8.3%)	
5	18 (90.0%)	2 (10.0%)		16 (80.0%)	4 (20.0%)	
6	32 (65.3%)	17 (34.7%)		26 (56.5%)	20 (43.5%)	
7	18 (42.9%)	24 (57.1%)		17 (41.5%)	24 (58.5%)	
8	19 (61.3%)	12 (38.7%)		15 (48.4%)	16 (51.6%)	
ICP monitoring						
Yes	81 (72.3%)	31 (27.7%)	0.236	70 (63.6%)	40 (36.4%)	0.012
No	135 (78.5%)	37 (21.5%)		128 (77.6%)	37 (22.4%)	
ICP						
<20 mmHg	41 (56.2%)	32 (43.8%)	<0.001	33 (47.1%)	37 (52.9%)	<0.001
≥20 mmHg	40 (93.0%)	3 (7.0%)		37 (86.0%)	6 (14.0%)	
CPP						
<60 mmHg	15 (88.2%)	2 (11.8%)	0.035	15 (88.2%)	2 (11.8%)	0.007
≥60 mmHg	53 (69.3%)	30 (36.1%)		46 (55.4%)	37 (44.6%)	
<70 mmHg	31 (79.5%)	8 (20.5%)	0.045	29 (74.4%)	10 (25.6%)	0.026
≥70mmHg	37 (60.7%)	24 (39.3%)		32 (52.5%)	29 (47.5%)	

High lighted data were the *p*-values without significant difference.
Poor prognosis: GOS 1–3.
Good prognosis: GOS 4–5.

Table 3. *GCS severity, ICP level, and CPP value influencing the mortality*

	Mortality before discharge			Mortality in 3 months F/U		
	Death	Survive	*p* value	Death	Survive	*p* value
GCS 3–5						
CPP <60 mmHg	7 (100.0%)	0 (0.0%)	<0.001	7 (100.0%)	0 (0.0%)	<0.001
CPP ≥60 mmHg	7 (26.9%)	19 (73.1%)		7 (28.0%)	18 (72.0%)	
CPP <70 mmHg	10 (62.5%)	6 (37.5%)	0.022	10 (62.5%)	6 (37.5%)	0.030
CPP ≥70 mmHg	4 (23.5%)	13 (76.5%)		4 (25.0%)	12 (75.0%)	
GCS 6–8						
CPP <60 mmHg	6 (60.0%)	4 (40.0%)	<0.001	6 (60.0%)	4 (40.0%)	<0.001
CPP ≥60 mmHg	3 (6.5%)	43 (93.5%)		3 (6.7%)	42 (93.3%)	
CPP <70 mmHg	6 (31.6%)	13 (68.4%)	0.028	6 (31.6%)	13 (68.4%)	0.031
CPP ≥70 mmHg	3 (8.1%)	34 (91.9%)		3 (8.3%)	33 (91.7%)	
ICP >20 mmHg						
CPP <60 mmHg	3 (60.0%)	2 (40.0%)	0.026	3 (60.0%)	2 (40.0%)	0.026
CPP ≥60 mmHg	9 (14.3%)	54 (85.7%)		9 (14.3%)	54 (85.7%)	
CPP <70 mmHg	4 (28.6%)	10 (71.4%)	0.251	4 (28.6%)	10 (71.4%)	0.251
CPP ≥70 mmHg	8 (14.8%)	46 (85.2%)		8 (14.8%)	46 (85.2%)	
ICP >20 mmHg						
CPP <60 mmHg	10 (83.3%)	2 (16.7%)	<0.001	10 (83.3%)	2 (16.7%)	<0.001
CPP ≥60 mmHg	3 (15.8%)	16 (84.2%)		3 (15.8%)	16 (84.2%)	
CPP <70 mmHg	13 (52.0%)	12 (48.0%)	0.006	13 (52.0%)	12 (48.0%)	0.006
CPP ≥70 mmHg	0 (0.0%)	6 (100.0%)		0 (0.0%)	6 (100.0%)	

High lighted data were the *p*-values without significant difference.
Mortality: GOS 1.
Survival: GOS 2–5.

Table 4. *GCS severity, ICP level, and CPP value influencing the outcome and prognosis*

	Outcome before discharge			3 months F/U outcome		
	Poor	Good	*p*-value	Poor	Good	*p*-value
GCS 3–5						
CPP <60 mmHg	7 (100.0%)	0 (0.0%)	0.219	7 (100.0%)	0 (0.0%)	0.099
CPP ≥60 mmHg	23 (88.5%)	3 (11.5%)		20 (80.0%)	5 (20.0%)	
CPP < 70 mmHg	16 (100.0%)	0 (0.0%)	0.039	15 (93.8%)	1 (6.3%)	0.033
CPP ≥70 mmHg	14 (82.4%)	3 (17.6%)		12 (75.0%)	4 (25.0%)	
GCS 6–8						
CPP < 60 mmHg	8 (80.0%)	2 (20.0%)	0.121	8 (80.0%)	2 (20.0%)	0.036
CPP ≥60 mmHg	25 (54.3%)	21 (45.7%)		20 (44.4%)	25 (55.6%)	
CPP < 70 mmHg	12 (63.2%)	7 (36.8%)	0.644	11 (57.9%)	8 (42.1%)	0.451
CPP ≥70 mmHg	21 (56.8%)	16 (43.2%)		17 (47.2%)	19 (52.8%)	
ICP <20 mmHg						
CPP <60 mmHg	3 (60.0%)	2 (40.0%)	0.847	3 (60.0%)	2 (40.0%)	0.593
CPP ≥60 mmHg	35 (55.6%)	28 (44.4%)		30 (47.6%)	33 (52.4%)	
CPP < 70 mmHg	7 (50.0%)	7 (50.0%)	0.620	7 (50.0%)	7 (50.0%)	0.902
CPP ≥70 mmHg	31 (57.4%)	23 (42.6%)		26 (48.1%)	28 (51.9%)	
ICP >20 mmHg						
CPP <60 mmHg	12 (100.0%)	0 (0.0%)	0.153	12 (100.0%)	0 (0.0%)	0.038
CPP ≥60 mmHg	17 (89.5%)	2 (10.5%)		15 (78.9%)	4 (21.1%)	
CPP < 70 mmHg	24 (96.0%)	1 (4.0%)	0.311	22 (88.0%)	3 (12.0%)	0.766
CPP ≥70 mmHg	5 (83.3%)	1 (16.7%)		5 (83.3%)	1 (16.7%)	

High lighted data were the *p*-values without significant difference.
Poor prognosis: GOS 1–3.
Good prognosis: GOS 4–5.

lower chances to survive ($p<0.001$). The CPP values maintained at levels higher than 60 or 70 mmHg both had better survival rates ($p<0.001$), and no significant difference in CPP was seen between the 60 and 70 mmHg groups.

As to the outcome before the discharge of patients from the hospital and the condition 3 months after the hospital stay, the results were quite similar (Table 2). For the patients age <50 Y/O, a higher GCS score, and ICP value maintained at level lower than 20 mmHg, it was enough to maintain CPP values of higher than 60 mmHg for a better prognosis ($p<0.05$ or 0.001). There was no further benefit in keeping a still higher CPP (≥70 mmHg) for such patients. However, the use of ICP monitoring showed no significant benefit for short term prognosis, while for the long term follow-up at 3 months, incorporation of ICP monitoring appeared to bring about better outcome ($p<0.05$).

We also classified the GCS severity into two groups: GCS 3–5 and 6–8 (Table 3). We found that maintenance of the CPP ≥60 or ≥70 mmHg both produced some benefits shown by higher survival rates no matter how severe the GCS was ($p<0.001$ or 0.05). For the CPP of higher than 70 mmHg, no further help was noted with regard to mortality. On the other hand, when we classified the patients according to ICP values of higher or lower than 20 mmHg, we found that to produce a lower mortality rate for he patients with ICP <20 mmHg, CPP ≥60 mmHg was enough ($p<0.05$) and the treatment with CPP ≥70 mmHg produced no better results. But if the ICP level was ≥20 mmHg, the CPP ≥70 mmHg did reduce the mortality further both during admission and at 3 months of follow-up ($p<0.001$ or 0.05).

Finally in Table 4, maintenance of the CPP value higher than 70 mmHg, for patients with GCS 3–5 produced a better prognosis than the CPP value maintained only higher than 60 mmHg ($p<0.05$). For patients with GCS 6–8, maintenance of CPP higher than 60 mmHg was good enough for long term follow-up ($p<0.05$). Therefore, it did not appear necessary to keep CPP ≥70 mmHg for patients with GCS 6–8. For patients with ICP <20 mmHg, nothing important was gained if the CPP level went beyond 70 mmHg. If the ICP level was ≥20 mmHg, maintenance of the CPP ≥60 mmHg was enough for long term outcome only, as with the patients with GCS 6–8 ($p<0.05$).

Discussion

Younger patients or the patients with less severe TBI should have better outcome and lower mortality [1, 2].

Implantation of an ICP monitor can reduce mortality for STBI patients, but in this study the outcome turned out better only in long term follow-up. However, if the ICP monitor was implanted for the STBI patient, the maintenance of ICP below 20 mmHg still helped the patients both in mortality and morbidity. ICP-oriented treatment for TBI patients has been the major principle of treatment in the past 10 years. The guidelines of head injury suggested the intracranial pressure threshold to be between 20 and 25 mmHg [13]. The results of our study showed that patients who were implanted with an ICP monitor improved both the survival rate and Glasgow Outcome Scale (Tables 1, 2). The results were comparable with regard to the previous report [3]. Therefore, it is still very important to implant an ICP monitor and to control ICP below 20–25 mmHg for STBI patients.

There was relative high mortality rate for the low GCS patients, around 80% [9]. Patients with GCS 3–5 are believed to have severe brain stem damages. We specifically divided patients into two subgroups: GCS 3–5 and GCS 6–8. In the GCS 3–5 subgroup, high CPP of $\geq$70 mmHg still improved the mortality rate both for the short term and long term outcome (Tables 3, 4) [9, 10]. For patients in the GCS 6–8 subgroup, CPP maintenance of $\geq$60 mmHg appear sufficient. It is obvious that the maintenance of CPP above 70 mmHg for patients with severe brain stem damage brought about significant improvement in outcome. In other words, the lower the GCS level, the higher the CPP should be.

In patients with ICP $\geq$ 20 mmHg, the benefits of high CPP ($\geq$70 mmHg) maintenance appear even more obvious as regards mortality. The aim of our study was focused on the CPP threshold in severe TBI patients. We divided the patients into two subgroups, according to ICP above or below 20 mmHg. In the ICP $<$ 20 mmHg group, maintenance of CPP $\leq$ 60 mmHg improved the survival rate, but not the functional aspect [8]. There was no additional benefit for patients with ICP $<$20 mmHg to maintain CPP of $\geq$70 mmHg. In addition, if the ICP was greater than 20 mmHg maintenance of CPP above 60 mmHg improved survival only ($p <$ 0.001). However the survival rate for these increased ICP patients was higher when CPP was kept $\geq$70 mmHg. The results were somewhat similar to Those of Lannoo *et al.* [6]. This suggests that the importance of maintaining CPP above 60 mmHg in increased ICP patients; maintenance of CPP at or above 70 mmHg for such IICP patients produced even better mortality control.

What is the optimal CPP? In 2000, cerebral perfusion pressure-orientated treatment for TBI suggested that adequate CPP must be kept greater than 70 mmHg, which however, was prone to produce adult respiratory distress syndrome because of excessive use of fluid and inotropic drugs for maintaining CPP [4]. The 2003 head injury treatment guidelines recommend that CPP has only to be maintained at a level greater than 60 mmHg. This study shows that maintenance of CPP higher than 70 mmHg was really necessary in some instances, such as low GCS and high ICP. Our results may help amend or recommendations in the 2003 guidelines for treatment of severe traumatic brain injury.

Conclusions

The maintenance of CPP above 60 mmHg was enough to prevent cerebral ischemia and further damages in most situations. But for patients with lower GCS 3–5, the CPP should be kept higher than 70 mmHg to produce lower mortality and better functional results. If complications of CPP maintenance at higher level can be avoided, the maintenance of CPP above 70 mmHg still should considered benefits of TBI patients.

Acknowledgements

The authors would like to acknowledge the grant from the Department of Health, Executive Yuan, Taiwan (DOH-TD-B-111-002), the grant (NHRI-EX97-9707PI, NHRI-CN-HD9503S) from National Health Research Institute, Taiwan, the grant (NSC 96-2314-B-038-010-MY2) from National Science Council, Taiwan, and the grant (96001-62-010) from Department of Health, Taipei, Taiwan.

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Acta Neurochir Suppl (2008) 101: 137–140

Printed in Austria

Hyper flow and intracranial hypertension in diffuse axonal injury: an update to gennarelli doctrine

M. Visocchi

Institute of Neurosurgery, Catholic University Medical School, Rome, Italy

Summary

Twelve consecutive paediatric (six) and adult (six) patients harbouring a neuroradiological pattern consistent with diffuse axonal injury (DAI) along with slit ventricles underwent haemodynamic study in the Intensive Care Unit of our University. All the patients had GCS scores less than 8 after a severe brain injury. serial head computed tomography (CT) and magnetic resonance (MR) scans demonstrated a radiological pattern of DAI. Transcranial Doppler Sonography (TCD) of the middle cerebral arteries was performed through the temporal bone window in all the patients. All patients but one underwent a continuous monitoring of intracranial pressure (ICP) and cerebral extraction of O2 (CEO2). Therapy with barbiturates and hyperventilation was necessary in all the cases. In two patients (one adult and one paediatric) a bilateral decompressive craniectomy was performed in order to decrease a severe intracranial hypertension. Hyperflow along with intracranial hypertension, variably responsive to barbiturate therapy, was observed in all the patients by means of TCD and CEO2. In our patients intracranial hypertension along with hyperflow syndrome were found associated with DAI. Medical as well as surgical treatments were tailored according to the haemodynamic study.

Keywords: Diffuse axonal injury; transcranial doppler sonography; brain swelling; cerebral hyperaemia.

Introduction

Primary traumatic axonal lesions with diffuse microscopic haemorrhagic lesions of the midline and subcortical grey matter belongs to DAI [21]. Differently from the concept of "secondary axonal injuries", delayed or secondary axotomy refers to delayed lesions in patients with functional DAI that evolve to structural DAI: defined as "diffuse axonal swelling secondary to tearing-torsion of encephalic nervous fibres" [11]. In this study we considered a sample of 12 patients harbouring immediate (1st day) radiological signs consistent both with diffuse axonal injury (DAI) and brain swelling (slit ventricles) in order to investigate on the haemodynamic and metabolic pattern associated with secondary brain insult. Associated to this basic pattern, haemorrhagic – necrotic lesions of the brainstem, most frequently of dorsolateral quadrants of rostral pons, of corpus callosum and adjacent structures (fornix, gyrus cinguli, septum pellucidum, nucleus caudatus and thalamus dorsalis), were described as well [10, 20].

The goal of the present study, according to the literature and to previous experiences of the author, is to find the possible pathohysiological mechanisms underlying such an intriguing disease along with the best therapy to be considered [14, 15, 20, 22, 23, 31, 32, 33].

Materials and methods

Twelve patients, eight males and four (age ranging from 4 to 32 years) admitted to the intensive care unit (ICU) after severe head trauma were considered for this study. Consciousness was impaired in all of them (Glasgow Coma Score (GCS) < 8 [13]. After early intubation, electrocardiogram (ECG), bones and chest X-rays examinations and blood serum standards, brain Computed Tomography (CT) was performed in all and repeated with magnetic resonance imaging (MR) the subsequent days. According to Marshall criteria the patients were classified as diffuse injury I: no visible pathology; diffuse injury II: minor midline shift and /or lesions; diffuse injury III: swelling; diffuse injury IV: major midline shift [20]. According to Gennarelli's criteria (MR) the patients were classified as grade 1: no macroscopic lesions; grade 2: focal lesions in the corpus callosum and white matter; grade 3: focal lesions in the dorsolateral quadrants of the rostral brainstem and same lesions of grade two [10, 11] (Table 1). All the patients underwent serial cerebral blood flow velocites recording by means of a TCD (Nicolet Biomedical NIC Vue Version 1.1.133, EME USA). A 2 MHz probe was put over the temporal windows in order to insonate both the middle cerebral arteries (MCA). Resistance indices (systo-diastolic ratio S/D, Gosling pulsatility index: PI = systolic – diastolic velocities/mean flow velocity) and mean flow velocity (systodiastolic/2) expressed in cm/sec were evaluated according to Aaslids' standards [1]. The MCA mean flow velocity and the internal carotid artery (ICA) mean flow velocity ratio (Lindegaard

Correspondence: Massimiliano Visocchi, M.D., Institute of Neurosurgery, Università Cattolica del S. Cuore, Lgo. A. Gemelli 8, 00168 Rome, Italy. e-mail: mvisocchi@hotmail.com

Table 1. *Neurological and instrumental evaluation*

Patient #/follow up	Age (yrs)	Sex	GCS	Lindegaard index/S j O2/ICP	CT/RM at admission	Lesion site
# 1/2.5 years	4	M	7	2.5/80%/no ICP monitoring	diffuse axonal injury, grade 2 brain swelling	callosum
# 2/10 years	6.3	F	7	2.3/85%/20 mmHg	diffuse axonal injury, grade 2 brain swelling	thalamus, callosum, corona radiata frontal lobe
# 3/9 years	7.7	M	6	2.2/89%/22 mmHg	diffuse axonal injury, grade 2 brain swelling	thalamus, callosum, basal ganglia
# 4/7 years	8.9	F	6	2/90%/25 mmHg	diffuse axonal injury, grade 3 brain swelling	thalamus, callosum, brainstem (focal)
# 5/3.5years	11.2	M	4	2/90%/22 mmHg	diffuse axonal injury, grade 3 brain swelling	thalamus, callosum, brainstem (focal)
# 6/2 years	15.6	F	4	1.8/95%/35 mmHg	diffuse axonal injury, grade 3 brain swelling	bilateral frontal lobe, brainstem (focal)
# 7/6 years	20	M	7	2.6/80%/23 mmHg	diffuse axonal injury, grade 2 brain swelling	callosum
# 8/2 years	29	M	4	2.4/85%/24 mmHg	diffuse axonal injury, grade 3 brain swelling	brain stem (focal)
# 9/8 years	23	M	5	2.1/85%/25 mmHg	diffuse axonal injury, grade 3 brain swelling	thalamus, brain stem
# 10/6 years	25	M	6	2.5/80%/23 mmHg	diffuse axonal injury, grade 2 brain swelling	basal ganglia
# 11/3years	30	M	7	1.9/85%/21 mmHg	diffuse axonal injury, grade 2 brain swelling	thalamus, callosum
# 12/6 years	32	F	7	1.5/90%/32 mmHg	diffuse axonal injury, grade 2 brain swelling	callosum, bilat. frontal lobe

index) were evaluated in all patients [6, 17, 18]. During the whole period of observation, metabolic parameters (pH, C02, 02) as well as the systemic haemodynamics (mean arterial blood pressure – MABP) were monitored and maintained within the limits of homeostasis. PaCO2 was simultaneously evaluated in all the patients along with TCD detection of CBF velocities by blood samples from the cubital vein. In order to evaluate the cerebral extraction of oxygen (CE02), i.e., the difference between the saturation of the arterial 02 (SaO2) and the one of the jugular 02 (SjO2), two 20 gauge polyurethane catheters were inserted percutaneously through the left radial artery and the left internal jugular bulb in all patients. According to the literature, mechanical ventilation was regulated aiming to assure a SjO2 ranging between 50 and 75% and CE02 between 24 and 45%; those values being considered within the "normal" range [12]. According to Martin, the combination of the Lindegaard Index < 3, the absence of dicrotic waves, the presence of bilateral TCD pattern and the Jugular O2 saturation $> 75\%$ was considered consistent with cerebral hyperflow [13, 35] (Table 1). Mannitol was administered in all the patients at the admission and suspended as soon as the diagnosis of hyperflow was suggested. In patient #6 and #12 when the diagnosis of intracranial hypertension was made mannitol was again administered. All patients received barbiturate therapy with thiopental sodium (1–5 mg/Kg/h for at least 36 h and not beyond one week) and were hyperventilated to maintain arterial pCO2 under 40 mm Hg. All the patients but one (pat #1 with severe slit ventricles at neuroradiological investigation) underwent a ventriculostomy for intracranial pressure (ICP) monitoring. Cerebro-spinal fluid (CSF) drainage was performed when ICP values were over 20 mm Hg. Two patients (#6; #12) underwent a bilateral decompressive craniectomy due to intracranial hypertension not responsive to the pharmacological therapy.

Results

A typical pattern of DAI ranging between grade two and grade three of Gennarelli's classification patients along with Marshall III diffuse injury were documented in all, immediately or soon after the admission. The Lindegaard index was constantly normal. All the patients with ICP monitoring had at least in one measurement more than 20 mm Hg. All the patients but two (#6; #12) showed a velocitometric pattern consistent with increased blood flow at admission. In the two cases (#6; #12), after a first phase of "normal" blood flow velocity (pulsatility index S/D and mean and systolic velocity within the limits) with normal ICP (phase 1) was followed by a second phase of increased flow velocity (low pulsatility index and S/D high mean and systolic velocity) associated to a rising of intracranial pression (phase 2) and by a third phase of markedly increased resistance indices (high pulsatility index and S/D), wave dicrotism and decreased blood flow velocity (phase 3) with persistent intracranial hypertension. After a drastic surgical manoeuvre (phase 4) with normalisation of ICP (decompressive craniectomy), the waveform pattern was then resembling to that of phase 2 until normalisation, was reached. Four days after craniectomy a normal TCD and metabolic pattern was reached (phase 5). In the other patients under examination the succession of all the phases could not be recorded; nevertheless an improvement (from phase 4 toward phase 1) or worsening (from phase 1 to phase 4) of the haemodynamic, metabolic and clinical pattern, were documented. Progression from

haemodynamic hyperflow pattern to normal was associated to the restoration of normal ventricular sizes; conversely progression from normal to hyperflow pattern associated to increased ICP values and slit ventricles pattern. The follow up of these patients ranges from 2 up to 10 years. At the maximum follow up available all the patients were markedly improved. Yet all patient still showed some neurological deficits.

Discussion

In 1982 Gennarelli and his group have shown that clinical and structural changes of DAI can be produced experimentally in subhuman primates using non-impact controlled angular acceleration of the head "in the absence of any increase in ICP or hypoxaemia" [2, 10, 11]. From 1989 some Authors correlated the increase of ICP, mortality and DAI [26]. Otherwise since 1998 others Authors proposed that patients with severe head trauma and DAI without associated mass lesion do not need ICP monitoring since "DAI is not associated with elevated ICP" [16]. The true nature of the so called "brain swelling" is still matter of debate. Despite in 1973 Bruce stated that diffuse cerebral swelling after a closed head injury can be due mainly due to cerebral hyperaemia and subsequent increase in cerebral blood volume (CBV), the Richmond's group, among others, has shown that intracellular oedema and not an increase in CBV is the main cause of brain swelling [3, 4, 19, 27, 28]. Nevertheless the acute cerebrovascular congestion or hyperaemia can also occur and, when present, is significantly related to intracranial hypertension and unfavourable outcome [5, 14]. In order to detect this pattern TCD has provided a rapid and non-invasive assessment of cerebral haemodynamics, especially blood velocity and pulsatility in the basal cerebral arteries; here is a proportional relationship between blood velocity and regional CBF when C02, CPP and brain metabolism are stable [30]. In 1990 Shigemori *et al.* found that increase of mean flow velocity in TCD recording is strongly related to the development of diffuse cerebral swelling [7, 29, 33]. Hyperaemia, when associated to severe head injury, can be found along with high intracranial pressure (ICP) as a consequence of an increase of intracranial volume; about 40% of brain swelling deteriorate to coma, develop neurological signs or complicate with an increase in ICP more likely in adults than in children . Such finding may lead to secondary haemorrhages especially after ICP decreasing maneuvers [24]. Impairment of cerebral autoregulation has been demonstrated in brain injured patients . In case of hyperflow due to loss of autoregulation, commonly seen in the so called brain swelling, the treatment of choice consists in a decreasing of the vascular bed as well as the blood volume; hyperventilation and barbiturates accomplish the "etiological therapy" of such a syndrome [33]. Otherwise one must be aware that osmotic therapy may increase CBF in vasoparalysis by decreasing blood viscosity [4, 9]. In 1993 Muttaquin first described 3 out of 35 cases of severe brain injury fulfilling the Gennarelli criteria of DAI with TCD findings consistent with hyperflow syndrome [22]. A secondary vascular involvement in severe brain injury is claimed as responsible for the appearance of vascular hyperemia and diffuse brain swelling complicated by an increase in ICP in 75% of the cases [52]. In 1995 and in 2002 and 2007 our group described different cases of DAI associated brain swelling with hyperflow syndromes as studied with TCD. In our opinion the prevalently median localization of the haemorrhagic lesions represents the radiological evidence of a centroencephalic convergence of shock waves [31, 32, 33]. The hypothalamic and brainstem reticular substance is located in the midline and it is the major site of regulation of cerebral circulation , consequently DAI macroscopic lesions close to these structures could be involved in TCD hyperflow patterns [24, 33]. According to Monro-Kellie doctrine on the constancy of intracranial blood volume, an increase of intracranial blood volume (i.e. vasomotor paralysis) produces an increase in ICP up to the progressive CBF reduction, resulting in the so-called "brain tamponade" [24]. Our observation confirm the role of hyperventilation, barbiturates and surgery (ventriculostomy and craniectomy when performed) in decreasing intracranial pressure and improving DAI patients [25]. Moreover , according to the present observation and some literature, we can state that brain swelling due to hyperflow can be observed in DAI patients and it can be associated with an increase in ICP. Finally TCD is a useful in assessing the cerebral autoregulation and CBF velocities in case of DAI , finally providing new perspectives to the original description of Gennarelli [29, 31, 32].

Acknowledgement

Supported by The Italian Society of Neurosonology and Cerebral Haemodynamics (SINSEC), The Italian Chapter of the European Society of Neurosonology and Cerebral Haemodynamics (ESNCH).

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Acta Neurochir Suppl (2008) 101: 141–144

Printed in Austria

Intracranial pressure fluctuation during hemodialysis in renal failure patients with intracranial hemorrhage

C. M. Lin[1,2], J. W. Lin[1,2], J. T. Tsai[3,4], C. P. Ko[1], K. S. Hung[1], C. C. Hung[5], Y. K. Su[1], L. Wei[1], W. T. Chiu[1,6], L. M. Lee[6,7]

[1] Department of Neurosurgery, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan
[2] Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[3] Institute of Biomedical Engineering, National Yang-Ming University, Taipei, Taiwan
[4] Department of Radiation-oncology, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan
[5] Department of Neurosurgery, Taipei Medical University Hospital, Taipei, Taiwan
[6] Graduate Institute of Injury Prevention and Control, Taipei Medical University, Taipei, Taiwan
[7] Department of Urology, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan

Summary

Coagulopathy in renal failure patients often makes them vulnerable to intracranial hemorrhage. Emergency decompression to remove the hematoma and to stop bleeding is always indicated. After the surgery, hemodialysis (HD) should be arranged to maintain the BUN/Cr. level, and I/O balance. During HD, intracranial pressure in all of the patients in this study fluctuated. This phenomenon always resulted in neurological deterioration in acute or chronic renal failure.

We present intracranial pressure (ICP) changes during HD in five acute or chronic renal failure patients with intracranial hemorrhage. They all underwent craniectomy or craniotomy with ICP monitors implantation. Different HD protocols were arranged for these patients and then we observed clinical results.

ICP elevated during HD and resulted in severe brain swelling. This situation was one of the clinical presentations of dialysis disequilibrium syndrome (DDS). Four patients died because of this complication and one survived. ICP fluctuation seemed to be correlated with the fluid amount and frequency of HD.

The prevalence and pathophysiology of DDS remain unclear. Renal failure patient with intracranial hemorrhage may be complicated with DDS when HD was performed. An attempt to reduce the fluid amount and to increase the frequency of HD might help these patients.

Keywords: Intracranial hemorrhage; dialysis disequilibrium syndrome (DDS); increased intracranial pressure (IICP); renal failure.

Introduction

Treatment for intracranial hemorrhage is very complicated, especially in patients with chronic or acute renal failure [4]. With coagulopathy, renal failure patients have higher risk to develop intracranial hemorrhage than others. When they have intracranial hemorrhage, renal failure patients have modest response to osmotic diuretics (such as mannitol, glycerol and/or sorbitol) in treatment for perifocal edema [13]. As the results, the renal failure patients have higher chances to require surgical decompression. After surgery, these patients undergo hemodialysis (HD) frequently. During the hemodialysis, gradually increased intracranial pressure (ICP) occurs. Intracranial hypertension often results in changes of consciousness, unstable vital signs, and incomplete or inadequate HD. Increased ICP is also the leading cause of mortality and morbidity in renal failure patients with intracranial hemorrhage. The HD related increased ICP and/or acute neurological deterioration are known as dialysis disequilibrium syndrome (DDS) [1, 6, 7, 15, 16, 18]. The prevalence and pathophysiology of DDS have seldom been reported in the past [1, 6, 7, 12]. We report our limited experience in this article to discuss the relationship between ICP fluctuations and HD in renal failure patients with intracranial hemorrhage. We also review the relevant literature on DDS.

Materials and methods

Clinical presentation of patients

From 2005 to 2006, we collected five patients of chronic renal failure with regular HD or acute renal failure after admission that underwent

Correspondence: Liang-Ming Lee, MD, Department of Urology, Taipei Medical University-Wan Fang Hospital; Graduate Institute of Injury Prevention and Control, Taipei Medical University; 111, Section 3, Hsing-Long Road, Taipei 116, Taiwan.
e-mail: k9_113@yahoo.com.tw

brain surgery for intracranial hemorrhage with ICP monitoring implantation. For maintenance of the BUN/Cr. Level and/or I/O balance, HD was arranged for all of them immediately after the brain surgery. We recorded the level of the ICP and used inotropic agents to maintain vital signs in a constant level during HD. All the clinical presentations are summarized below and in Table 1.

Patient 1: A 56 year-old male patient had a history of uremia under regular HD for ten years. He had subdural hemorrhage (SDH) secondary to stercotactic aspiration of brain abscess. After the hemorrhage, the Glasgow Coma Score (GCS) deteriorated from $E_3M_6V_4$ to $E_2M_4V_E$. As the results, he underwent decompressive craniectomy with removal of hematoma and ICP monitor insertion. After the surgery, ICP was kept below 20 mm Hg, but there was a drastic elevation of ICP when he received HD.

Patient 2: A 67 year-old male patient had a history of uremia under regular HD for six years. He suffered from head injury that resulted in SDH. Before surgery, the GCS was $E_1M_4V_E$. He underwent decompressive craniectomy and ICP monitor insertion. After the surgery, increased ICP was found during HD from the first to seventh day after operation.

Patient 3: A 6 year-old boy, following a traffic accident, developed SDH and epidural hemorrhage (EDH) in the left temporal region. Before surgery, the GCS score was $E_1M_1V_E$. Then he underwent emergency decompressive craniectomy and ICP monitor implantation. Because of acute renal failure secondary to rhabdomyolysis, he received HD for three days after the surgery, complicated by increased ICP and bilateral pupillary dilatation during HD.

Patient 4: A 56 year-old female patient with uremia had received regular HD for seven years. She suffered from sudden onset of consciousness loss. The brain CT scan revealed left thalamic hemorrhage, intraventricular hemorrhage, and acute hydrocephalus. Before emergent surgery, the GCS score was $E_1M_4V_E$. She underwent external ventricular drainage with ICP monitoring. After operation, she was found to have increased ICP during HD.

Patient 5: A 24 year-old male patient, after a traffic accident, had traumatic subarachnoid hemorrhage (SAH) and SDH in the right frontotemporal region with midline shift. The GCS was $E_1M_5V_2$. Then he had decompressive craniectomy and ICP monitoring. Due to acute renal failure and rhabdomyolysis, he received HD after the surgery. We used continuous venous-venous hemodialysis (CVVH) during the first day for HD followed by a decreased fluid amount and higher frequency of HD. No increased ICP during HD was found in this patient.

Dialysis protocol

In our study, patient 1 to 4 received regular HD every other day (Model number: TORAY TR-321 EX). During the HD, no heparin was used for fear of rebleeding, and the HD process was conducted with 200 ml/min flow rate for 4 h till the total of 5% body weigh fluid was dialyzed. Diaslysate solution A and B (hemodialysis concentrate No.11, Ca 3.0 and Hemodialysis solution 300 GB, Taiwan Biotech Co. Ltd) were used in this regular protocol.

Patient 5 received CVVH in the first day for 24 h with GAMBRO PRISMA CRRT system. The CVVH dialysate Solution A and solution B (Taiwan Biotech Co. Ltd) were applied with 120/min flow rate. The total amount of dialyzed fluid was 5% of body weight. The subsequent everyday HD procedure was the same like in regular HD protocol but with a different flow rate (100 ml/min) and the same duration. The total amount of dialyzed fluid was 2.5% of body weight.

Results

The mean ages were 41.8 ± 23 years. There were four males and one female. The GCS score for all of these patients before surgery were less than 8. Among those patients with intracranial hemorrhage, three received HD because of end stage renal disease, and two because of acute renal failure secondary to rhabdomyolysis. Patients 1–4 received HD with the regular procedure

Table 1. *Clinical features of patients with intracranial hemorrhage*

Case No.	Age	Body weight (kg)	Sex	Diagnosis	Surgery type	History of dialysis (years)	Dialysis type	Renal failure	GCS on admission (E, M, V)	Outcome
1	56	67	M	SDH	Craniectomy	10	HD	Chronic	7 (2, 4, 1)	Death
2	67	60	M	SDH	Craniectomy	6	HD	Chronic	6 (1, 4, 1)	Death
3	6	26	M	SDH; EDH	Craniectomy	–	HD	Acute	3 (1, 1, 1)	Death
4	56	38	F	ICH; IVH	EVD	7	HD	Chronic	6 (1, 4, 1)	Death
5	24	53	M	SAH; SDH	Craniectomy	–	CVVH and HD	Acute	8 (1, 5, 2)	Survive
Mean ± SD	41.8 ± 22.96	48.8 ± 14.91				4.6 ± 3.98			6 ± 1.67	

SDH Subdural hemorrhage, *EDH* Epidural hemorrhage, *ICH* Intracerebral hemorrhage, *IVH* Intraventricular hemorrhage, *EVD* External ventricular drainage, *HD* Hemodialysis, *CVVH* Continuous venous-venous hemodialysis, Mean ± *SD* Mean ± standard deviation.

Table 2. *Correlations between ICP, mean arterial blood pressure, fluid amount of HD, and timing on HD*

Case No.	Mean ± SD of ICP during HD	Mean ± SD of MABP during dialysis	Fluid amount of dialysis (L)	Duration of dialysis (hours)
1	23.2 ± 7.63	133.56 ± 11.04	2.5	4
2	23 ± 4.05	91.08 ± 9.07	2.5	3.5
3	32.4 ± 9.31	70.92 ± 9.78	0.4	2.5
4	39.4 ± 6.83	104.5 ± 12.34	2.1	3.5
Mean ± SD			1.875 ± 0.87	3.375 ± 0.54

ICP Intracranial pressure, *MABP* Mean arterial blood pressure, *HD* Hemodialysis, Mean ± *SD* Mean ± standard deviation.

and patient 5 received CVVH and different HD protocol (Table 1).

During the HD, BP maintenance was performed with infusion of inotropic agents. The amount of fluid dialysed was determined by the vital signs during the HD and total I/O for each patient. The HD was performed as slowly as possible, for at least 3 h, except in patient Number 3. For this patient, we stopped the HD 2.5 h after initiation because of the unstable vital signs and great difficulty in maintenance (Table 2).

Patient 1–3 and 4 died because of central failure, and increased ICP during HD. Figure 1 shows ICP change during HD in patients 1–3, and 4. They all received HD by the standard method (HD every other day). In these patients, ICP began to rise in the first hour of HD and reached the peak gradually around the end of the second hour. The ICP was above thresholds in all cases and resulted in poor outcome. A number of retrospective studies have reported ICP 20 mm Hg as a cut-off point between patients with potentially good or poor outcomes [5, 13]. The ICP returned to the condition before dialysis 4 h after discontinuation of the HD (Fig. 1).

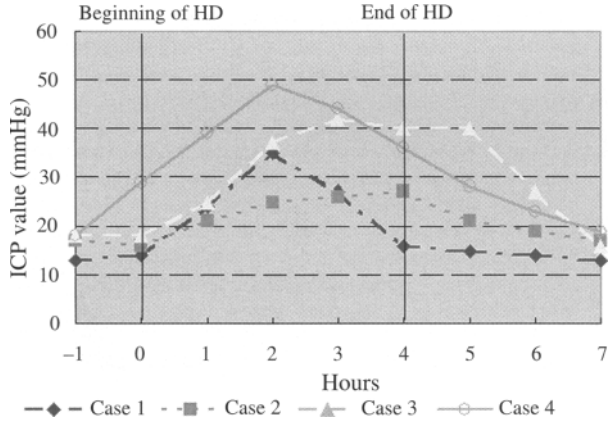

Fig. 1. ICP level changes of patients No: 1–4 during the HD. The ICP level fluctuated above the normal range rapidly and then dropped back to normal after HD gradually

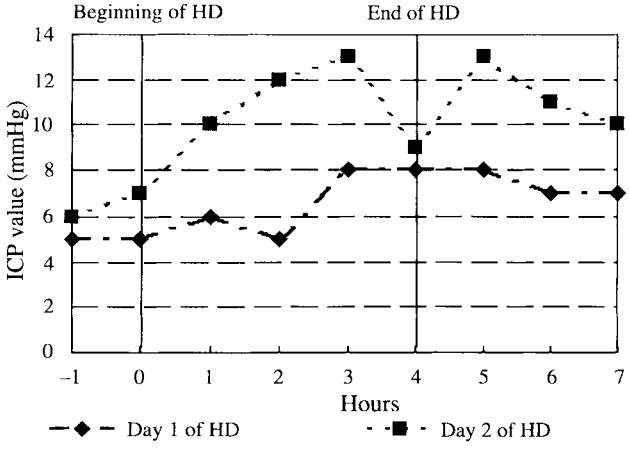

Fig. 2. ICP level changes of patient 5 during the first and second days of HD. The same duration with half speed made the fluid amount of HD decrease to half. As the fluid amount decreased, the HD frequency should be increased to every day. With this protocol the ICP level was kept within the normal range

Patient 5 received HD because of acute renal failure and rhabdomyolysis. This patient received different HD procedure. We used CVVH in the first day and relatively stable ICP was noted (Fig. 2). In the following days, we tried to decrease the fluid amount of HD to half within the same HD duration and to increase the frequency of HD to everyday. ICP was not beyond thresholds among this everyday protocol (Fig. 2). Thereafter, this patient made a good recovery and returned to previous daily activities one month later.

Discussion

DDS is the clinical presentation of acute neurologic dysfunction attributed to cerebral edema that occurs during or following HD. DDS occurs most commonly following initiation of HD for patients with end-stage renal disease [1]. We found that relationships existed between increased ICP and HD in all chronic or acute renal failure patients. Patients with pre-existing neurologic disease, such as head trauma, stroke, or malignant hypertension, may be at greater risk for developing DDS [12, 18]. The precise DDS prevalence is poorly defined and may be underestimated due to the wide spectrum of clinical presentations.

The DDS pathogenesis remains controversial, but two central hypotheses have been proposed. The first, acute urea removal occurs more slowly across the blood-brain barrier than from plasma. The resulting concentration difference generates a reverse osmotic gradient that shifts water into the brain, and results in cerebral edema [16]. Absolutely increased water content in the brain has been proved in the rat model of uremia. When rapid HD was applied to this model, an increased urea concentration ratio was also found in the rat brain and plasma [14, 15]. Furthermore, down-regulation of central nervous system urea transporters in uremic patients was also proved as a possible mechanism contributing to the delay urea clearance in the brain [8].

The second, increased osmolality of the extracellular fluid in uremic patients stimulates an adaptive accumulation of intracellular organic osmolytes to protect the cerebral neuron from dehydration [3]. During the HD, retention of these organic osmolytes contributes to par-

adoxical reduction in intracellular pH, and results in increased brain osmolality and cerebral edema [2, 17].

In this study, ICP fluctuation did not increase significantly in the first hour of HD, but elevated drastically within the second hour (Fig.1). And then the ICP reached the peak consequently two hours after the beginning of HD. This phenomenon of DDS was not related to blood flow change. Even though we maintained adequate cerebral perfusion pressure and stable BP with inotropic agents in patient 1, 2, and 4, the increased ICP persisted.

Preventing DDS is the mainstay of therapy for HD, particularly during the initial phase of HD in post-operative patients. Despite the absence of evidence-based guidelines, the ultimate goal of preventing DDS is to perform a gradual clearance of urea. This can be achieved with different HD protocols, such as using of a smaller, less efficient dialyzer and/or reducing the duration of initial dialysis to about two hours with lower blood flow rates (<150 mL/min). By use of sustained low-efficiency dialysis (SLED) or initiation of continuous venous-venous hemodialysis (CVVH), more gentle clearance of urea might be achieved to decrease the DDS risk in renal failure patients with intracranial hemorrhage [1, 9–11].

Conclusion

The prevalence and pathophysiology of DDS remain unclear. In renal failure patients, HD may contribute to DDS and increased ICP when patients have intracranial hemorrhage. This study was limited by a small sample size to produce reliable coefficients, but we would still recommend to reduce the fluid amount and to increase frequency of HD in order to prevent DDS in acute or chronic renal failure patients with intracranial hemorrhage.

Acknowledgements

The authors would like to acknowledge the grant from the Department of Health, Executive Yuan, Taiwan (DOH-TD-B-111-002), the grant (NHRI-EX97-9707PI, NHRI-CN-HD9503S) from National Health Research Institute, Taiwan, the grant (NSC 96-2314-B-038-010-MY2) from National Science Council, Taiwan, and the grant (96001-62010) from Department of Health, Taipei, Taiwan.

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Acta Neurochir Suppl (2008) 101: 145–149

Printed in Austria

Effect of hyperbaric oxygen on patients with traumatic brain injury

J. W. Lin[1,2], J. T. Tsai[3,4], L. M. Lee[5,6], C. M. Lin[1,2], C. C. Hung[7], K. S. Hung[1], W. Y. Chen[1], L. Wei[1], C. P. Ko[1], Y. K. Su[1], W. T. Chiu[1,6]

[1] Department of Neurosurgery, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan
[2] Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[3] Institute of Biomedical Engineering, National Yang-Ming University, Taipei, Taiwan
[4] Department of Radiation-oncology, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan
[5] Department of Urology, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan
[6] Graduate Institute of Injury Prevention and Control, Taipei Medical University, Taipei, Taiwan
[7] Department of Neurosurgery, Taipei Medical University Hospital, Taipei, Taiwan

Summary

Hyperbaric oxygen therapy (HBOT) is the medical therapeutic use of oxygen at a higher atmospheric pressure. The United States Food and Drug Administration have approved several clinical applications for HBOT, but HBOT in traumatic brain injury (TBI) patients has still remained in controversial. The purpose of our study is to evaluate the benefit of HBOT on the prognosis of subacute TBI patients. We prospectively enrolled 44 patients with TBI from November 1, 2004 to October 31, 2005. The study group randomly included 22 patients who received HBOT after the patients' condition stabilization, and the other 22 corresponding condition patients were assigned into the matched control group who were not treated with HBOT. The clinical conditions of the patients were evaluated with the Glasgow Coma Scale (GCS) and Glasgow Outcome Scale (GOS) before and 3 to 6 months after HBOT. The GCS of the HBOT group was improved from 11.1 to 13.5 in average, and from 10.4 to 11.5 ($p < 0.05$) for control group. Among those patients with GOS = 4 before the HBOT, significant GOS improvement was observed in the HBOT group 6 months after HBOT. Based on this study, HBOT can provide some benefits for the subacute TBI patients with minimal adverse side effects.

Keywords: Traumatic brain injury; hyperbaric oxygen; Glasgow Coma Scale (GCS); Glasgow Outcome Scale (GOS).

Introduction

Traumatic brain injury (TBI) is a major cause of death and disability. Every year in the United States, there are about one million head-injured people treated in hospital emergency rooms, and roughly 50,000 people die from TBI [8], 230,000 people are hospitalized, and 80,000 survive with significant disabilities. Because of the enormous medical expenditure resulting from such injury, many efforts have been devoted to minimize the influence of TBI.

Clinically, there are two mechanisms directly related to the TBI outcome. The first one is the primary insult, which results from the impact itself, and all the neuronal damages are determined by the impact. As this insult has already occurred before the patient comes to hospital, there is little that a medical team can do for the patient. The second mechanism is the delayed non-mechanical, which results from tissue edema after the impact followed by ischemic change inside the brain. This theoretically preventable or treatable condition is the principal target of treatment for TBI. All the medical treatment should therefore be devoted to minimize edema and facilitate cerebral blood flow, to enhance cerebrovascular autoregulation, to reduce cerebral metabolic dysfunction, and to adequately maintain cerebral oxygenation [7]. Furthermore, excitotoxic cell damage and inflammatory process resulting from ischemia may also lead to increased cell death [12]. Generally speaking, about 80% of deaths in TBI result from hypoxia. Consequently, oxygen supplement in the initial resuscitation of a TBI patient is of paramount importance.

Hyperbaric oxygen therapy (HBOT) is the medical use of oxygen at a pressure exceeding atmospheric pressure (ATA). The mechanism of HBOT consists in drastically increasing oxygen partial pressure of the tissues,

Correspondence: Wen-Ta Chiu, M.D., Ph.D., Department of Neurosurgery, Taipei Medical University-Wan Fang Hospital; Graduate Institute of Injury Prevention and Control, Taipei Medical University; 111, Section 3, Hsing-Long Road, Taipei 116, Taiwan.
e-mail: wtchiu@tmu.edu.tw

and facilitating the oxygen transport by plasma. As a result, HBOT can improve oxygen supply to the injured brain and diminish the volume of brain that will necrotize during ischemia [5, 11].

Materials and methods

In this prospective cohort study, we intended to study the impact of HBOT on moderate to severe TBI patients. The protocol of this study was approved by the Investigation Review Board-Wanfang Medical Center (approval no. F950305). All the patients were enrolled under the regulation of inclusion and exclusion criteria, and the criteria were as follows.

Inclusion criteria

1. Age ≥16 y/o (Pediatric patient was excluded).
2. The patients were diagnosed to have moderate to severe TBI. (Glasgow Coma Scale (GCS) from 3 to 12).
3. TBI condition stabilization.
4. Stable vital sign and spontaneous respiration without endotracheal intubation or mechanical ventilation (tracheotomy was eligible for the enrollment).
5. No active infection or leucocytosis.
6. A hyperbaric oxygen department physician was consulted, and he (she) agreed to treat the patient with HBOT.
7. Informed consent could be obtained from the patient's family.

Exclusion criteria

1. Medical history with central nervous system disease (e.g. Parkinson disease, dementia, congenital anomaly, stroke... etc.)
2. Systemic disease history (e.g. diabetes, coronary artery disease, renal insufficiency, COPD... etc.)
3. Multiple traumas (e.g. Chest contusion, abdominal blunt injury, internal bleeding, pelvic fracture... etc.)
4. Skull base fracture with CSF rhinorrhea or otorrhea.
5. Smoking or alcoholism.
6. Hemoglobin ≤10 gm/dl for female or ≤12 gm/dl for male patients.

When the patients were enrolled, the assignment will be decided. If one patient was chose randomly to be a study group candidate then there will be another patient with corresponding condition (e.g. age, sex, clinical course, severity and condition... etc.) chose to be the matched control group patients. If the patient was chose to be the study candidate, the potential risk and benefit will be explained to the family for the obtaining of the treatment consent. From Nov. 1, 2004 to Dec. 31, 2006, there were total 62 patients enrolled into his study. Finally, there were 44 complete patients' data available for the further analysis.

In this research, we used a multi-user pressurized chamber (Model no.: BTG/875/PV/02GOC-100, Apex Process Technologies (S) PTE LTD, Singapore) to treat patients. The HBOT protocol was to apply two-hour, two ATA pressures in the process. We increased the air chamber pressure slowly to 2 ATA over 15 min and maintained this pressure for 90 min. Patients were given 100% oxygen with O_2 masks. Then we depressurized to normal ATA over 15 min. The full treatment course was defined as once a day for 20 days over a 4 week period. [9] During the HBOT the patients' condition and vital sign were closely monitored. If there was any complication (e.g. hypotension, short of breath, seizure, unstable vital sign (blood pressure increased or decreased larger than 20 mmHg), hypoxia ($SaO_2 < 95\%$)... etc.) happened during HBOT, the treatment for this patient will be discontinued, and this patient and the corresponding controlled one will be excluded. The purpose of our study was to clarify the influence on HBOT in subacute TBI patients by analyzing patients' demographic information, GCS changes, and comparing variables such as the GCS, the injury severity, and the length of time of HBOT, with regard to the subacute TBI outcome. And the TBI outcomes were evaluated with the Glasgow Outcome Scale (GOS) consisting of 5 levels (1: Death, 2: Vegetative status, 3: Severe disability, 4: Moderate disability, and 5: Good recovery).

After data collection, we analyzed the result with SPSS 11.0 software. We compared the two groups by means of demographic information, including sex, age, body weight, injury timing, the severity of head injury, duration of hospital stay, treatment with received surgery or that without surgery, and length of HBOT treatment time. We compared the GCS and GOS scores of both groups at different times with the Chi-square test to assess difference between the two groups. The patients were stratified with different GOSb levels (GOS level before the HBOT) (GOSb = 2, GOSb = 3, and GOSb = 4). There was no GOSb = 1 and the GOSb = 5 patients enrolled because GOSb = 1 patients died before the

Table 1. *Demographic information for patients*

	HBOT group	Control group
Total	22	22
Sex		
M:F	19:3	19:3
Age		
Below 24	7	5
25–64	13	16
Above 65	2	1
Body weight (kg)	61.75	65.12
GCS		
9–12	10	10
3–8	12	12
Diagnosis		
EDH	3	2
SDH	5	6
ICH	4	5
SDH+ICH	5	4
SAH	3	4
DAI	2	1
Surgery		
With	16	20
Without	6	2
GOSb		
4	7	6
2–3	15	16

GCS The patient initial GCS during admission.
GOSb The patient's GOS before HBOT or the same time for the control group (mean 27.5 days after head trauma).
All variables have $p > 0.05$.
EDH Epidural hematoma, *SDH* subdural hematoma, *ICH* intracerebral hemorrhage, *SAH* subarachnoid hemorrhage, *DAI* diffuse axonal injury.

Table 2. *GCS improvement for the patients after HBOT*

	GCS mean on arrival	GCS mean before HBOT	GCS mean after HBOT
HBOT group	8.0	11.1	13.5
Control group	7.9	10.4	11.5*

* $p < 0.05$ with significant difference.

Table 3. *GOS outcome for the patients 3 and 6 months after HBOT*

		GOS3a without improvement	GOS3a with improvement	GOS6a without improvement	GOS6a with improvement	Total
GOSb = 2	HBOT	8	3	7	4	11
	control	8	2	7	3	10
GOSb = 3	HBOT	2	2	2	2	4
	control	4	2	3	3	6
GOSb = 4	HBOT	3	4	1	6*	7
	control	3	3	3	3	6
Total		28	16	23	21	44

GOSb The patient's GOS before the HBOT or the same timing for the control group.
GOS3a The patient's GOS at 3-month post injury or at the same timing for control group.
GOS6a The patient's GOS at 6-month post injury or at the same time for control group.
* $p < 0.05$ with significant difference.

HBOT and there was nothing could be improved for GOSb = 5 patients. We recorded the GOS scores before (GOSb) and 3 (GOS3a) and 6 (GOS6a) months after HBOT or at the same time for the control group patients to evaluate performance of the patients.

Results

As showed in Table 1, 22 patients were enrolled in each group. The M:F sex ratio was the same: 19:3 in both groups. Most of the patients were aged between 25 and 64 years, which was also the most common range of age for head injury. The average interval from injury to receiving HBOT was 27.5 ± 5.8 days. This was also the timing for the first GOS evaluation for both groups. If the patients received HBOT, the average treatment times were 24.4 ± 7.8 times. In this table, no significant difference was found in age, sex, body weight, GCS severity, presence or absence of surgical intervention, or GOS severity between HBOT and control groups (all $p > 0.05$).

The average initial GCS scores for both groups' patients on arrival were 8.0 and 7.9, respectively. After admission, surgical and/or medical treatments were applied to these patients, and the GCS recovery from 8.0 to 11.1 and from 7.9 to 10.4, respectively. We applied HBOT to the patients after their traumatic condition stabilization, and there was considerable improvement in the HBOT group, from 11.1 to 13.5. In the control group, GCS improved only from 10.4 to 11.5. Even in this subacute stage of TBI, HBOT showed beneficial effects on GCS improvement for moderate or severe TBI patients ($p < 0.05$) (Table 2).

The patients in both groups were stratified with the GOSb level (GOSb = 2, 3, and 4) to evaluate the HBOT effects on TBI patients. The outcome at the third and sixth months after the HBOT was evaluated and analyzed. In third month evaluation (Table 3), even though there was some improvement in patients with HBOT, the numbers were not sufficient for drawing significant difference and conclusion between study and control groups.

In sixth month evaluation (Table 3), there were 12 patients with improvement in the HBOT group, and 9 patients in the control group, but the difference did not reach statistically significance ($p > 0.05$) for GOSb = 2 or 3 patients. However, there was a significant difference between these two groups among patients with GOSb = 4, and as a whole the GOS6a (6 months after HBOT) improvement was greater in the HBOT group than in the control group ($p < 0.05$).

Adverse event

Two patients developed seizures during the first week of HBOT, and the convulsions were controlled with anticonvulsants. Then the patient resumed HBOT 2 weeks later. Two patients experienced severe ear pain, and received tympanostomy. Thereafter the ear pain subsided, and the patient completed the full course of HBOT successfully. No pulmonary adverse event, unstable vital sign, or cataract occurred during HBOT or within 6 months follow-up. However, all these 4 study candidates and their corresponding control patients were excluded.

Discussion

The US Food and Drug Administration have approved several clinical applications for HBOT. They included certain non-healing wounds, radiation necrosis of soft tissue and radiation osteonecrosis, carbon monoxide poisoning, decompression sickness, acute arterial ischemia, and some sports injuries. These approvals did not include TBI. However, in the literature review; we found reports showing some supports for HBOT application to TBI patients.

In 2004, the Agency for Healthcare Research and Quality reviewed two fair-quality trials [1, 10], showing fair evidence that HBOT might reduce mortality or the duration of coma in severe TBI patients. But in one of the trials, HBOT also implicated an increased chance for poor functional outcome. Therefore, the evidences were conflicting. Although these two trials are cited frequently, the methodologies of these two trials are also criticized [6]. In the past, HBOT was used under the concepts of improving TBI patients' outcome and mitigating social economical expenditure [2]. Previous studies have been focused on the immediate use of HBOT after head trauma. However, during the initial period of TBI, patients are often ventilator-dependent and may have other associated injuries, such as lung contusion. Under such situation, it is not convenient to treat TBI patients with HBO early. With SPECT to show blood flow improvement and to analyze them with different age groups, Golden et al, reported that HBOT could improve cerebral metabolism in the chronic stage of TBI [4]. There are only limited data in the literature to support beneficial effects of HBOT on TBI patients with different degrees of severity.

In some animal study [7], using 2.5 ATA HBOT could reach maximum microcirculatory hemoglobin oxygen saturation and 2 fold of normal hemoglobin circulation but there was also higher complication, such as pulmonary system barotrauma, cataract, glaucoma, seizure ... etc. [6, 10, 11]. The Rockswold *et al.* reported that using 1.5 ATA HBOT for 60 min is relatively safe without any oxygen toxicity [5, 11]. In our series, we used HBOT with 2 ATA for 90 min every day for a total 20 times. What the optimal oxygen atmospheric pressure and duration used in HBOT is need further clarification.

The timing of using HBOT around one month (27.5 ± 5.8 days) after TBI is more practical in clinical condition. At that stage, patients have become more stable for their cardiopulmonary function and often have received intensive rehabilitation. As a consequence, the frequency of HBOT-related respiratory complications will be reduced. Furthermore, the synergistic effect of rehabilitation with HBOT conceivably triggers the improvement of the patient's GOS in the sixth month.

The adverse events in this trial were rare. Only two patients had seizures during the initial period of HBOT, and another two had middle ear barotrauma. The seizure incidence in the previous reports was 2.4 per 10,000 patient-treatments [13]. Because the population base was different between our results and this report, and we focused on the head trauma patients only, there should be higher incidence of seizure attack during the HBOT. Besides, the sample size of our patients was too small for statistical comparison. The tympanic membrane tear is common in HBOT [3]. However, in our HBOT center, tympanoplasty was not routinely performed before HBOT; this simple procedure should be considered and performed before the HBOT to reduce the patient's suffering. As the minor side effects, such as tinnitus, aural fullness, disequilibrium, and vertigo and or nausea, these side effects were all well tolerated by the patients [9].

In this trial, we demonstrated that the GCS of TBI patients in the HBOT group recovered significantly better than in the control group ($p<0.05$) (Table 2). This result would indicate that HBOT has a positive benefit in GCS recovery of TBI patients. For the GOS improvement, there was no obvious difference, especially for the 3 months follow-up (Table 3). Why did GCS improve so much, and GOS did not? GOS is widely applied for TBI patient outcome evaluation, but the intervals used for GOS scores are too rough. In recent studies, an extended GOS was used to evaluate the outcome of the TBI patients, and more detailed evaluation might help our future study.

For the patients receiving HBOT, there was no improvement of GOS in the third month follow-up, but 6 months after HBOT, GOSb = 4 group got some improvement (Table 3). This situation could be explained by the delayed effect of HBOT. That means HBOT needs some more time to express the effects.

The TBI patients with GOSb = 4 showed significant GOS improvement six months after HBOT in the study group ($p<0.05$, Table 3). But there was no such difference in the GOSb = 2 or GOSb = 3 groups. In GOSb = 2 (vegetative state) and GOSb = 3 (severe disability) patients, there should be severe parenchymal damages in the cerebral cortex. HBOT can not regenerate necrotic neurons, but can only improve reoxygenation of the brain parenchyma. With incorporation of rehabilitation, HBOT can help patients with mild neurological deficits to recover and return to normal life. In this prospective study, we can conclude that HBOT can help TBI patients in GCS recovery and also help patients with mild functional disability to lead a better life.

Acknowledgements

The authors would like to acknowledge the grant from the Department of Health, Executive Yuan, Taiwan (DOH-TD-B-111-002), the grant

(NHRI-EX97-9707PI, NHRI-CN-HD9503S) from National Health Research Institute, Taiwan, the grant (NSC 96-2314-B-038-010-MY2) from National Science Council, Taiwan, and the grant (96001-62-010) from Department of Health, Taipei, Taiwan.

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Acta Neurochir Suppl (2008) 101: 153–155

Printed in Austria

Treatment of adjacent vertebral fractures following multiple-level spinal fusion

J. C.-C. Wu[1], C.-T. Tang[2], D.-L. Wu[2], T.-H. Tsai[2], Y.-H. Chiang[1]

[1] Department of Neurosurgery, Taipei Medical University Hospital, Taipei Medical University, Taipei, Taiwan
[2] National Defense Medical Center, Department of Neurological Surgery, Tri-Service General Hospital, Taipei, Taiwan

Summary

Background. Posterolateral fusion with cages and posterior instrumentation is an accepted method in the treatment of lumbar instability associated with spinal stenosis or scoliotic deformity, but with modest results. We propose hereby an alternative, simple method to treat kyphosis due to the vertebral fracture which has brought about comparable outcomes.

Methods. Three patients with documented adjacent segment compression fractures were treated. Vertebroplasty was performed with polymethylmethacrylate (PMMA), either using the transpedicular route at the adjacent level or *via* the route of the previous transpedicular screw at the top level of the long-segment fixation construct. Outcomes were measured by the visual analogue scale of pain and the kyphotic angle of the adjacent segment.

Results. The maximal kyphotic angle was 30.6 degrees preoperatively and the reduction rate averaged 69.6%. The pain scale improved from the mean of 9.3 to 1.7. No further progression of compression was noted in the follow-up of more than 6 months after the vertebroplasty in these cases.

Conclusion. Vertebroplasty at either the adjacent level or the top level of the previous internal fixation construct may be a feasible alternative to treat the adjacent level fracture after long segment internal fixation of the spine.

Keywords: Vertebroplasty; vertebral body; transpedicular fixation; fracture; long segment.

Introduction

Compression fracture at the last instrumented level or adjacent segment vertebral body after multilevel fusions has previously been reported to be a frequent complication [2]. Contributing factors emphasized to induce these compression fractures in response to rigid instrumentation have previously been documented [5, 6, 8]. Reoperation with extension of the internal fixation construct has been the accepted counter measure [7]. Thanks to recent advancement and acceptance of percutaneous transpedicular vertebroplasty with polymethylmethacrylate (PMMA) in treatment for compression fracture, we have been able to utilize this method as a treatment option for symptomatic adjacent level compression fracture. To the best of our knowledge, this is the first article to report vertebroplasty as an effective treatment for the symptomatic vertebral fracture after long-segment internal fixation.

We discuss the treatment options and outcomes of three patients, all of whom had undergone long-segment internal fixation for degenerative lumbar disease, and whose vertebral body fracture developed several months after the initial open lumbar fusion procedure.

Correspondence: Yung-Hsiao Chiang, Department of Neurosurgery, Taipei Medical University Hospital, 252 Wu-Hsing Street, Taipei 110, Taiwan. e-mail: ychiang@tmu.edu.tw

Methods

Three patients with documented adjacent segment compression fractures were treated by vertebroplasty using polymethylmethacrylate (PMMA) either *via* the transpedicular route at the adjacent level or *via* the route of previous transpedicular screw at the top level of the long-segment fixation construct. Outcomes were measured by the visual analogue scale of pain and the kyphotic angle of the adjacent segment.

Results

Case 1

A 64-year-old woman with progressive claudication and mild lower limb weakness and low back pain previously received laminofacetectomies with instrumentation and posterior lateral fusion. After return of ability to walk and a pain-free interval of 3 months, the patient began to

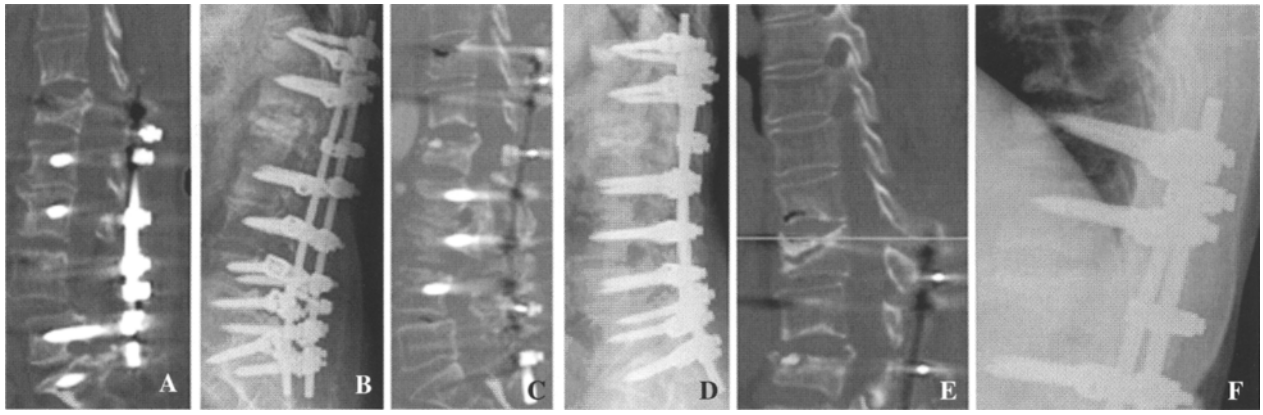

Fig. 1. 64/F initially with 6-level fusion (L2-S1), (A) referred due to progressive bone collapse, L1, VAS:9. (B) After extending the internal fixation construct to include T11, 12; (C) further collapse of T11 occurred in months. (D) Cement augmentation at T11 alleviated pain temporarily, (E) then collapse of T10 occurred. (F) After final cement augmentation of T10, VAS decreased to 1

experienced excruciating back pain and a plain radiograph showed compression fracture at the top level (L1) of the previous spinal fusion construct (Fig. 1A). Pain was relieved after extension of the previous long-segment fixation construct to include T11 and T12 (Fig. 1B).

Two months later, pain recurred and compression fracture progressed at anterior superior body of T11 (Fig. 1C). Symptoms were once again controlled with vertebroplasty *via* the route of the previous screw (Fig. 1D). One month later, painful T10 compression fracture occurred (Fig. 1E), and vertebroplasty was performed at the anterior inferior portion of the T10 vertebrae (Fig. 1F).

Case 2

This 75-year-old male was admitted due to progressive back pain and difficulty walking for a year. Lumbar surgery involving posterior lateral fusion and instrumentation from L2 to L5 was performed previously and an attempt to remove the construct was abandoned due to pedicular screw breakage. Patient was admitted under the impression of top level and adjacent level (L1, L2) compression fracture (Fig. 2A) and spinal stenosis at L1–2 due to ligamentum flavum hypertrophy. Laminectomy with removal of the ligamentum flavum was performed with subsequent removal of the L2 screw and injection of PMMA *via* the route of previous screw insertion. Vertebroplsty was also performed at L1 with direct injection of PMMA into anterior inferior portion of the vertebral body. Pain improved after the last operation from a pre-operative pain scale of 9 to post-operative pain scale of 2.

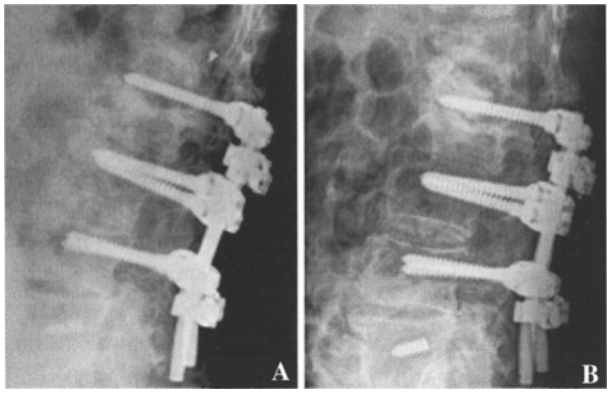

Fig. 2. 76/M initial 4-level fusion, L2–L5, (A) referred due to progressive bone collapse, L1 and L2. (B) After cement augmentation, VAS:9 – > 2

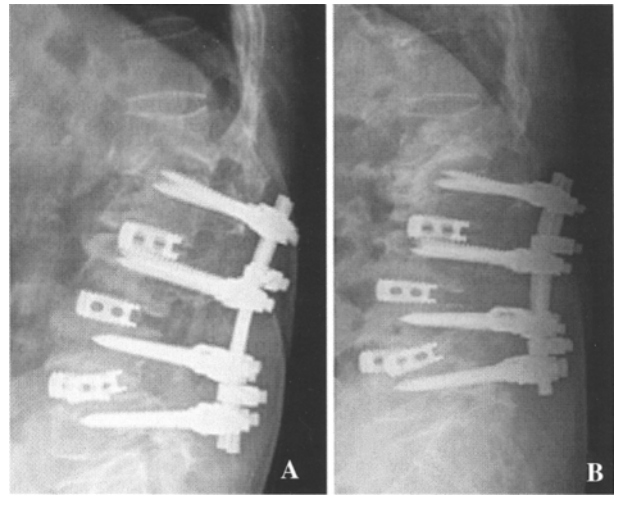

Fig. 3. 71/F initial 4-level fusion, L2–L5, (A) progressive bone collapse of L1 and L2 was noted. (B) After cement augmentation, VAS:10 – > 2

Case 3

This 72-year-old female with radiating pain, claudication and weakness of lower limbs underwent posterior lumbar interbody fusion and transpedicular instrumentation from L2 to L5. Weakness and pain subsided after the fusion procedure and remained alleviated for about a year. Pain recurred about one year after the first operation, and was considered to be due to compression fracture of L2–L5. Vertebroplasty was performed at L1 bilaterally with injection of PMMA into the anterior inferior cavity, PMMA redistributed during injection and extended to the anterior superior portion of L2. Pain improved after the operation from the pre-operative pain scale of 10 to the post-operative pain scale of 2.

In these cases, the average pre-operative kyphotic angle was 30.6° and the post-operative kyphotic angle 9.3°. No recurrence of pain or compression fracture were noted for at least 9 months after the last vertebroplasty.

Discussion

Transpedicular fixation, although taken for the golden standard for lumbosacral arthrodesis, has its share of complications. Common complications include infection and instrument failure [7]. Adjacent level vertebral body fracture is another common complication and occurs in nearly one third of cases after fixation for degenerative instability [3, 7]. Studies have show decreased bone mineral density in the vertebral body superior to or at the levels of the fusion [5, 6]. Treatment options of these adjacent level fractures has been rarely reported in publications due to poor outcome of these patients [2]; however, treatment with elongation of instrumentation has been suggested as an option for these patients when they are symptomatic [7].

Elongation of instrumentation, however, appears to have its limitations. In the first case, the initial satisfactory outcome was thwarted by yet another adjacent level fracture. Although this complication may be disposed of as another unfortunate sequala, it is an illustration of further adjacent level fractures caused by longer segment fusion procedures. An increase in bone stress is associated with a longer instrumentation due to the modified load sharing, and ultimately, elongating the instrumentation to treat adjacent level fracture could result in propensity in further adjacent level fractures.

While vertebroplasty was effective in relieving pain for all patients in this study, it was also associated with further adjacent level fractures. Some biomechanical studies suggest that fractures in adjacent, non-augmented vertebrae are due to maximum filling with cement in restoration of the stiffness and strength of the vertebral body [1], while other studies blame bone marrow density, not the pattern of augmentation, as the main cause of further fractures. These fractures are, however, reported to be reduced by extension of augmentation to include levels of low bone marrow density [4].

Elongation of the long-segment internal fixation construct was not considered for the second and third cases. Since studies suggest that extension of augmentation should include levels with low bone marrow density, and decreased bone mineral density was suspected in the vertebral body superior to or at the levels of the fusion [1, 4–6], PMMA augmentation was performed at the top level and adjacent level. For the third case, the cavity of the adjacent level and the top level vertebrae were connected, and PMMA was successfully injected into these cavities *via* the adjacent level.

Conclusion

This is probably the first report demonstrating vertebroplasty as another feasible option to relieve pain due to top-level and adjacent-level compression fracture as a result of long-segment lumbar fusion. Further studies are needed to confirm the beneficial effects of this method.

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Acta Neurochir Suppl (2008) 101: 157–160

Printed in Austria

Clinical and radiographic results of unilateral transpedicular balloon kyphoplasty for the treatment of osteoporotic vertebral compression fractures

S.-B. Lee, K.-S. Cho, P.-W. Huh, D.-S. Yoo, S.-G. Kang, D.-S. Kim, C.-K. Park

Department of Neurosurgery, Uijongbu St. Mary's Hospital, The Catholic University of Korea College of Medicine, Uijongbu, Korea

Summary

Introduction. Most previous reports indicate that traditional bilateral kyphoplasty improves patient function and restores height of collapsed vertebral bodies, but limited data about the effects of unilateral kyphoplasty on clinical and radiological outcome are available.

Material and methods. One hundred five patients were treated by unilateral kyphoplasty between January 2004 and December 2006. These patients underwent 105 operations to treat 132 vertebral compression fractures between T8 and L5. Sagittal alignment was analyzed from standing radiographs. Clinical outcomes were determined by comparison of preoperative and postoperative data from patient-reported index (visual analogue pain scale score). Radiographs were assessed as to percent vertebral collapse, vertebral height restoration and local kyphosis correction.

Results. Mean length of follow-up was 15.3 months (range 3–36 months); improved height 2.3 and 4.0 mm in the anterior and medial columns, respectively ($P > 0.05$); Cobb angle increased 3.0° ($P < 0.05$), visual analogue pain scale score improved from 8.7 ± 1.4 before surgery to 2.3 ± 0.9 ($P < 0.05$); no adverse medical or procedural complications; 6.8% (9/132) cement leakage rate.

Conclusion. Unilateral transpedicular kyphoplasty improves physical function, reduces pain, and may correct kyphotic deformity associated with vertebral compression fractures. This result shows comparable to traditional bilateral kyphoplasty procedure.

Keywords: Unilateral transpedicular kyphoplasty; vertebral compression fracture; osteoporosis; kyphosis; deformity correction.

Introduction

Compression fractures lead to a loss of height of the vertebral segment, and the resulting spinal deformity can lead to a decrease in pulmonary capacity, malnutrition, decreased mobility, and depression [4, 5, 9, 11]. Balloon kyphoplasty is a recently developed, minimally invasive surgical treatment for osteoporotic vertebral compression fractures (VCFs). The deformity is purportedly corrected by the insertion and expansion of a balloon in a fractured vertebral body. Good clinical outcomes as well as restoration of vertebral body height have been reported with kyphoplasty [3, 6, 7, 10]. The current standard technique for kyphoplasty involves cannulating both pedicles and placing 2 balloons into the vertebral body (bipedicular approach). Theoretically, an alternative unipedicular approach would reduce by 50% the risk associated with cannulation of the pedicles, while also reducing operative time, radiation exposure, and costs.

We experienced 105 compression fractures patients and performed kyphoplasty in 132 levels *via* a unilateral transpedicular approach. The purpose of the this study is to describe the performance of a procedure known as inflatable bone tamp *via* a unilateral transpedicular approach and determine the efficacy of unipedicular transpedicular approach and the clinical and radiological outcomes.

Material and methods

A consecutive series of one hundred thirty two osteoporotic VCFs were treated in 105 patients between January 2004 and December 2006 in our institute. Eighty (76%) patients were women and 25 (24%) were men. Mean patient age was 71.6 years (range, 49–85 years). The fractures occurred between T8 and L5. Ninety-five patients had a single vertebral fracture treated by kyphoplasty, and 10 patients had multiple vertebral levels treated by kyphoplasty (2–3 vertebrae).

Operative technique

The patient was carefully positioned prone on the fluoroscopy table. After incision of the skin, an 11-gauge Jamshidi needle was placed through the left-side pedicle into the posterior vertebral body. Special care was taken to achieve a medial trajectory of the needle and a final midline position of the needle tip in the vertebral body (Fig. 1). Cement

Correspondence: Kyoung-Suok Cho, M.D., Department of Neurosurgery, Uijongbu St. Mary's Hospital, The Catholic University of Korea College of Medicine, Uijongbu 480-130, Korea. e-mail: kscho@catholic.ac.kr

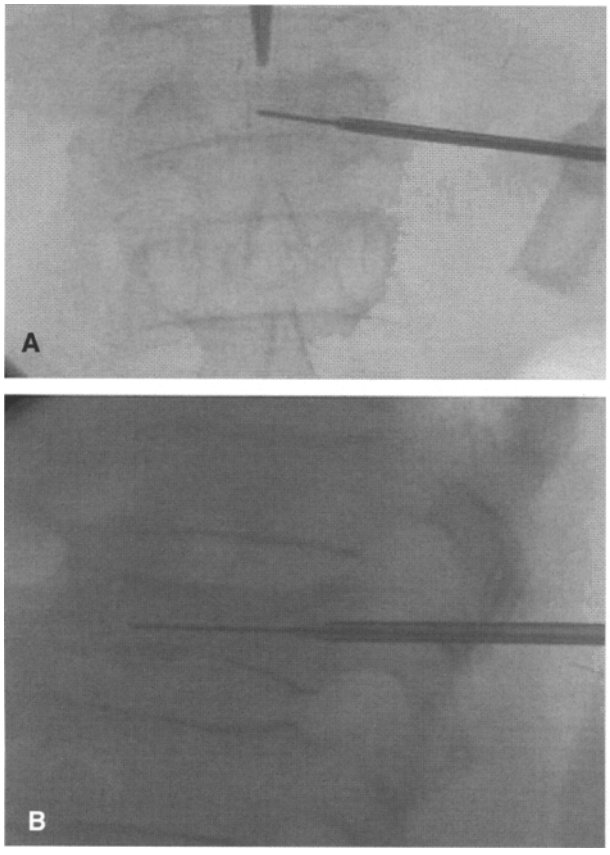

Fig. 1. (A) Antero–posterior image of inflatable bone tamp in the midline of the fractured vertebral body and (B) tip of the guide pin should place over the center of the vertebral body in the lateral image

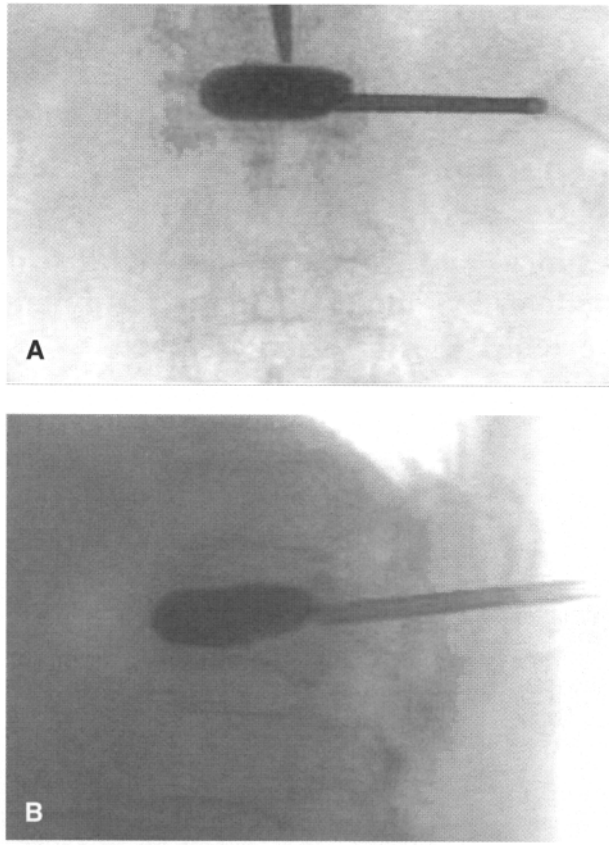

Fig. 2. (A) Anterior–posterior and (B) lateral fluoroscopic image of polymethylmethacrylate filling the cavity within the fractured vertebral body

was administered which produced an excellent filling of the vertebral body cavity (Fig. 2A, B).

Assessment of kyphosis and vertebral body height

The vertebral body kyphotic angle (Ka) [(Ka) was the angle in degrees defined by the intersection of lines *ef* and *gh*] was calculated using the Cobb technique. For determination of the Cobb angle, measurements were taken from the superior endplate of the vertebra one level above the treated vertebra to the inferior endplate of the vertebral body one level below the treated vertebra (lines *ab* and *cd*). Vertebral height (H) of the fractured vertebra was the distance between identical points on the superior and inferior endplates at the middle (Hm) and anterior (Ha) location (Fig. 3).

Outcome measure

Postoperative complications were recorded prospectively at surgery. Patients rated their pain on a visual analogue scale of 0 = no pain to 10 = severe pain before surgery, and immediate postoperative 3 day later when discharged.

Results

We performed unilateral transpedicular kyphoplasty in 105 osteoporotic compression fracture patients for 3 years at our institute. The fracture morphology was a wedge in 101 patients and burst in 4 patients. Fractures were classified as acute in 94 and chronic in 11 patients. The mean duration of symptoms was 4.5 weeks (range, 1–24 weeks). All fractures were considered active on T2-weighted chemical fat suppression or short tau inversion recovery MR sequences.

Overall reduction of vertebral deformity

The Cobb angle improved significantly from $-14.8° \pm 8.1°$ before surgery to $-11.8° \pm 9.0°$. Every patient achieved at least a reduction of 3°. An improvement of at least 5° in sagittal alignment was achieved in 48 patients. Kyphotic angle improved significantly from $-12.8° \pm 6.1°$(range, $-19.3°$–$4.4°$) before surgery to $7.1° \pm 4.7°$ (range, $-15.4°$–$5.8°$) after surgery. Height of fractured body (Ha, and Hm) improved significantly from $19.8\,mm \pm 0.24$ (range, 10.8–31.7) to $22.1 \pm 0.16\,mm$ (range, 11.7–32) and from $18.5\,mm \pm 0.18$ (range, 10.5–28.7) to $22.5 \pm 0.15\,mm$ (range, 13.2–29.1) (Table 1). The mean operation time was less than 35 min.

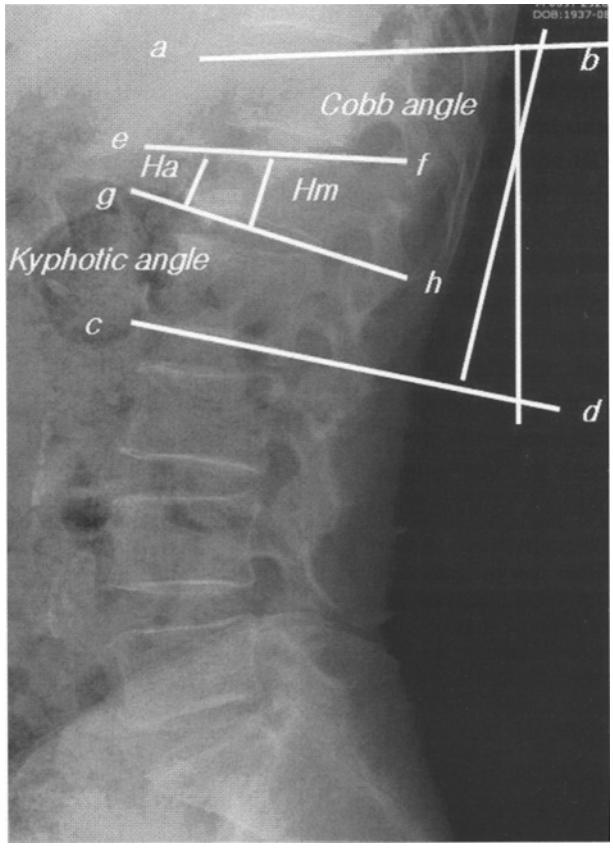

Fig. 3. Measurement of Cobb angle (line *ab* and *cd*), kypotic angle (linc *ef* and *gh*), height of fracture middle (*Hm*), and anterior (*Ha*) vertebral height

Table 1. *Cobb angle, kyphotic angle and veterbral body height (Ha, Hm) improved significantly after kyphoplasty procedure*

	Preoperative	Postoperative	Regain	
Cobb angle	−14.8°	−11.8°	3°	20%
Kyphotic angle	−12.8°	−7.1°	5.7°	44%
Average ant. Ht (Ha)	19.8 mm	22.1 mm	2.3 mm	7%
Average mid. Ht (Hm)	18.5 mm	22.5 mm	4 mm	13%

Clinical outcome

Evaluation of intraoperative and postoperative radiographs revealed extravertebral cement leaks in 9 of 132 vertebral fractures treated (6.8%). In 9 cases, cement leaked into the adjacent intervertebral disc and in 8 patients, cement leaked into the spinal canal in 1 patient. None of the cement leaks had any apparent clinical consequences, and no patients developed neurologic symptoms. Virtually all patients subjectively reported immediate relief of their typical fracture pain. The VAS score significantly improved from 8.7 ± 1.4 (range, 2.9–10) before surgery to 2.3 ± 0.9 (range, 0.3–4.2) after surgery.

Discussion

The results of the present study indicate that kyphoplasty is a minimally invasive procedure aimed at restoring strength, stiffness and is effective in reduction of spinal deformity and in short-term improvement of pain in selected patients with osteoporotic vertebral compression fracture.

Previous studies have been suggested that unipedicular kyphoplasty might lead to unilateral wedging or that it would not be as effective in restoring vertebral body height [1, 2, 8]. Steinmann *et al.* in an *ex vivo* biomechanical study comparing a bipedicular approach to unipedicuar approach in the treatment of vertebral compression fractures, found no significant lateral wedging associated with unipedicular injections [8]. Our study found that the unipedicular approach is effective in restoring the vertebral height. In our cases, vertebral body height was successfully restored by unipedicular kyphoplasty to 96% of fracture levels. Furthermore, kyphoplasty by unipedicular approach markedly reduced pain and spinal deformity with osteophorotic vertebral compression fracture.

Kyphoplasty may have an increased risk of pedicle fracture that can lead to spinal compression. It is associated with breakage of the pedicle during insertion of the cannula. Theoretically, the incidence of such events may be reduced if unilateral rather than bilateral cannulas are placed. By cannulating only 1 pedicle, one can reasonably assume a considerable reduction in operative time, radiation exposure, and cannulation risks with the unipedicular kyphoplasty when compared to the bipedicular approach. In the procedure that we have described, the time required for the procedure was less than 35 min and also save the cost about 30% comparing to the bipedicular approach. Typically, when we have performed with bilateral approach, the total procedure time is close to one hour. We are sure that unilateral transpedicular approach has excellent clinical and radiographic outcome and is comparable to bipedicular approach.

The key to unilateral approach is the medial trajectory of the needle and the final midline position of the balloon.

Conclusion

Unilateral transpedicular pedicular kyphoplasty is comparable to bipedicular kyphoplasty in the restoration of vertebral body strength, stiffness, and height in vertebral compression fractures. Given the advantages of a unipedicular approach with respect to vertebral pedicle can-

nulation risk, operative time, radiation exposure, and cost. This study would support the use of a unilateral transpedicular approach to kyphoplasty in the treatment of osteoporotic vertebral compression fractures.

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Acta Neurochir Suppl (2008) 101: 163–168

Printed in Austria

Radiosurgery from the brain to the spine: 20 years experience

A. A. F. De Salles[1,2], A. A. Gorgulho[1], M. Selch[2], J. De Marco[2], N. Agazaryan[2]

[1] Division of Neurosurgery, David Geffen School of Medicine, University of California at Los Angeles, CA, USA
[2] Department of Radiation Oncology, David Geffen School of Medicine, University of California at Los Angeles, CA, USA

Summary

Introduction. Radiosurgery evolved from brain to spine. Mechanical and computer advances in linear accelerator (LINAC) radiosurgery apply precise single/fractional stereotactic radiation to multiple pathologies.

Methods. During a 10-year span the senior author used proton-beam radiosurgery in over 300 lesions, followed by gamma-knife, adapted and dedicated LINACS, including cyber-knife, in another 700 patients. The last 10 years, experience was accumulated with the Novalis in over 3,000 patients. Novalis uses a beam-shaper in a high-speed delivery LINAC. It operates using conventional circular arc, conformal static beam, dynamic conformal or intensity modulated modes. Patients treated with Novalis at the UCLA since 1997 were evaluated regarding effectiveness, complications and failure. These results were compared with previous 1997 data.

Results. Over 4,000 patients with trigeminal neuralgia/intractable pain, arteriovenous malformations/angiomas, metastases, ependymomas, gliomas, meningiomas hemangiopericytomas, schwannomas, adenomas, hemangioblastomas, and chordoma were treated. Spinal lesions were treated with frameless stereotaxis and on-line precision checks. Treatment was expeditious, comfortable and with reduced complications. Success is similar or superior to published data. Reduced treatment time of complex lesions and highly homogeneous dose compares favorably to other radiosurgery.

Conclusions. The senior author's experience validates the novel shaped-beam approach. Long-term follow-up supports safety and effectiveness and capability to treat brain and spine.

Keywords: Proton beam; linear accelerator; gamma-knife; radiosurgery; spine.

Introduction

During a span of 20 years, starting in 1986, the senior author had the opportunity to work and observe the development of several generations of stereotactic radiosurgery devices. Initially using the Proton Beam at the Harvard Cyclotron, the senior author had the opportunity to adapt modern imaging, MRI and CT scan to stereotactic radiosurgery. Largely dedicated to the treatment of arteriovenous malformations and pituitary adenomas, approximately 300 patients were treated per year. The concepts of on line imaging confirmation and fusion were present in the Proton Beam stereotactic room serving as the bases to the modern stereotactic radiosurgery devices and planning tools [3].

The Gamma Unit, already present at the University of California since 1982, had shown the importance of Radiosurgery worldwide with the units in Stockholm, Buenos Aires and Sheffield. It gained greater popularity with the work of the stereotactic group at the University of Pittsburgh starting in 1987. After experiencing radiosurgery with the Linear Accelerator using the relocatable Laitinen's stereotactic device at the University of Umea in 1988 and 1989 [20], it became clear to the author that the versatility of linear accelerators would have major impact in the applications of stereotactic radiosurgery, mostly with the possibility to add stereotactic radiotherapy [6] and spinal radiosurgery [8]. At the University of California the author used initially the gamma unit and further adapted linear accelerators to radiosurgery.

Methods

One thousand patients treated during the first 10 years of the author's experience using proton beam radiation in over 300 lesions, followed by gamma-knife [36], adapted linear accelerators to radiosurgery including cyberknife [1] and dedicated linear accelerators in another 700 patients comprise the first group of patients. This experience is compared with the last 10 years data accumulated with shaped beam stereotactic radiation throughout the nervous system in over 3000 patients.

Currently a beam shaper device mounted permanently to a high speed radiation delivery LINAC (800 monitor units) coupled with frameless stereotactic navigation system and on line imaging verification of target

Correspondence: Antonio A. F. De Salles, M.D., Ph.D., Division of Neurosurgery, 200 UCLA Medical Plaza, Suite 504, Los Angeles, CA 90095-7039, USA. e-mail: adesalles@mednet.ucla.edu

is used at UCLA (Novalis, BrainLab Heimstetten, Germany). This system has been described previously [35]. Patients treated at the University of California Los Angeles since 1997 were evaluated regarding effectiveness, development of radiosurgery complications and early failure of treatment. These results were analyzed in comparison with previous data of the same author. Technical aspects of proton beam, adapted, dedicated and shaped beam linear accelerator radiosurgery and stereotactic radiotherapy, as well as robotic linear accelerator radiosurgery have been extensive reported by the author and his group [1, 5, 8, 16, 19, 25, 28–30, 32, 34, 35, 38].

Results

Over 4000 patients were treated, including over 200 functional cases of trigeminal neuralgia, intractable pain, and areteriovenous malformations, cavernous angiomas, metastases, ependymomas, gliomas, meningiomas, hemangiopericytomas, schwannomas, pituitary adenomas, hemangioblastomas, chondrosarcoma and cordomas.

Demonstration of the treatment plan using state of the art imaging and target location is presented in Fig. 1. The 5 mm collimator isocenter is currently placed at the root entry zone of the trigeminal nerve affected with the 50% isodose line touching the surface of the brainstem. The dose is 90 Gy at 100%, i.e., maximal dose and the 45 Gy reaching the surface of the brainstem [18].

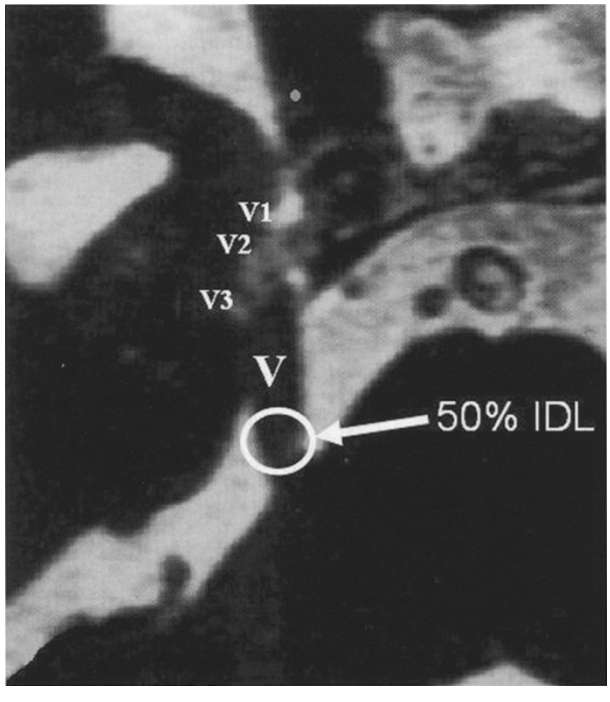

Fig. 1. Visualization of the trigeminal complex with magnetic resonance imaging using constructive interference steady state (CISS). Notice the target location at the root entry zone. The 50% isodose line touches the brainstem as demonstrated by the *arrow*. The dose use is 90 Gy to the target point, not to the volume demonstrated. 45 Gy touches the surface of the brainstem

Sphenopalatine ganglion is targeted for complex regional facial pain and cluster headache using the same dose prescription and collimator [12]. Functional targets in the brain such as thalamotomy [15] and cingulotomy are treated with 140 Gy, again using the 5 mm collimator, although the 3 mm collimator has also been used, making discrete and precise lesion [7].

Small arteriovenous malformations are treated with conformal single isocenter, homogeneous dose distribution and prescription with the 90% isodose line in the periphery of the lesion. Spetzler and Martin classification correlates well with the success rate of radiosurgery for this lesions, Grade 2 reaches 100% response while the Grade III reaches 60%. All Grade I AVMs are treated with surgery at UCLA [10]. Grade IV and Grade V AVMs reach 30% response rate, while VI reaches 60% [26]. The use of shaped beam radiosurgery reduced the complication rate from 5% [27] to transient complication of 2.5% [26]. Combined embolization is used in a trial of decrease AVM volume [14], however the main objective of embolization has been to treat arteriovenous fistulas present in the nidus, as well associated aneurysms. Currently stereotactic radiotherapy is used to decrease the volume of a large AVM, grade IV and V to again treat after a follow up of 3 years with radiosurgery. The pilot data of this approach shows a decrease in volume of giant AVMs of a mean of 72%, ($n = 20$). Figure 2 shows such an AVM that was treated with the protocol of 6 fractions of 5 Gy and stereotactic radiosurgery with 15 Gy at the 4 year follow up.

Initially as adjuvant therapy for skull base meningiomas [4], radiosurgery and stereotactic radiotherapy evolved as the techniques of choice in selected meningiomas locations [28]. Acoustic neuroma radiosurgery evolved from single dose only to small tumors to a trial a hearing preservation with stereotactic radiotherapy with a scheme of 2 Gy in 26 fractions. This approach has allowed preservation of 93% of useful hearing with a follow up of 3 years. The size decrease and absence of growth is observed for 100% of the tumors treated. Therefore the freedom of surgery after stereotactic radiotherapy has been 100%. Facial nerve deficit is less than 1% at this time [32]. The evolution of treatment was to bring maximal function preservation with maximal control rate. Single dose radiation is still used in patients who have lost hearing at the time of diagnosis, as with single dose of 12 Gy preservation of useful hearing was 60% in our hands.

Pituitary adenomas are approached first surgically, stereotactic radiosurgery is always offered when the op-

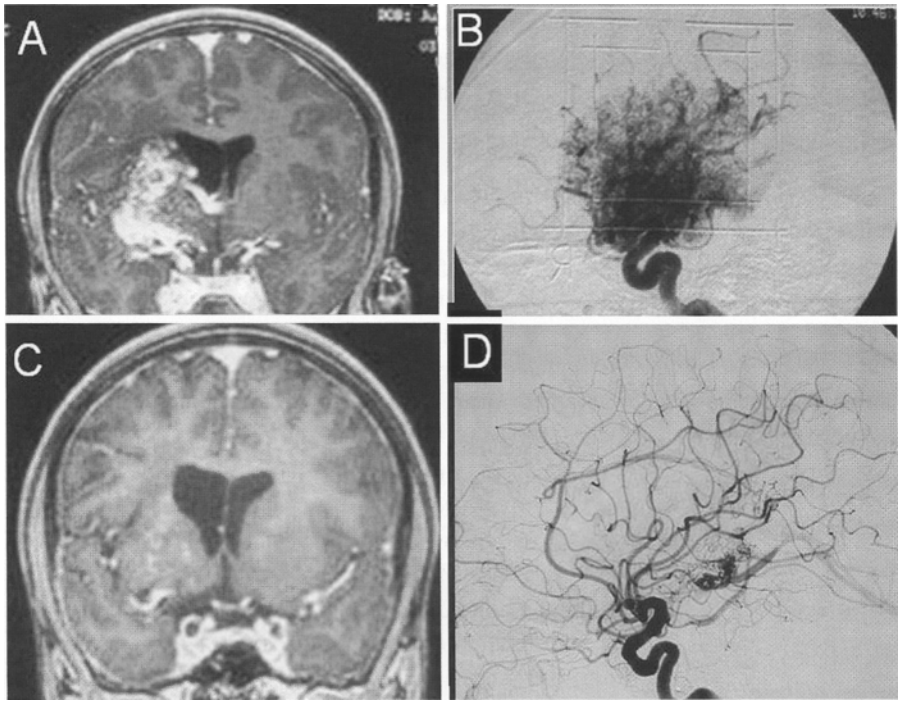

Fig. 2. (A) T1 Magnetic resonance image with gadolinium enhancement showing the giant basal ganglia AVM before stereotactic radiotherapy. (B) Lateral cerebral angiogram showing the lesion at the time of the treatment (6 Gy in 5 consecutive fractions). (C and D) Show the 4 year follow up, time of the radiosurgery of 15 Gy

tic apparatus is away from the tumor, at least 3 mm distance. Single dose is always preferred when hormonal burden is present. Stereotactic radiotherapy is offered when the optic apparatus is involved in non secreting tumors. The crude control rate of non secreting tumor with stereotactic radiotherapy has been 100% [30]. Craniopharyngiomas reached a three-year actuarial survival rates free of solid tumor growth or cyst enlargement of 94% and 81%, respectively [29]. Follow up as long as 9 years have shown that the cyst can recur even at this long term follow-up (Fig. 3).

Chordomas are treated with stereotactic radiotherapy to bring the dose to 72 Gy in fractions. Single dose is used with small residual and for boost when possible after stereotactic radiotherapy. Moderate length follow up has shown a control rate of 100 [25]. At longer follow-up (unpublished data) the control rate has held at 72%.

Since 1990 the preferred management of intraparenchimal matastases has been Radiosurgery. The presence of less than four lesions and no mass effect calls for radiosurgery. Innumerous lesions or lesion reaching the

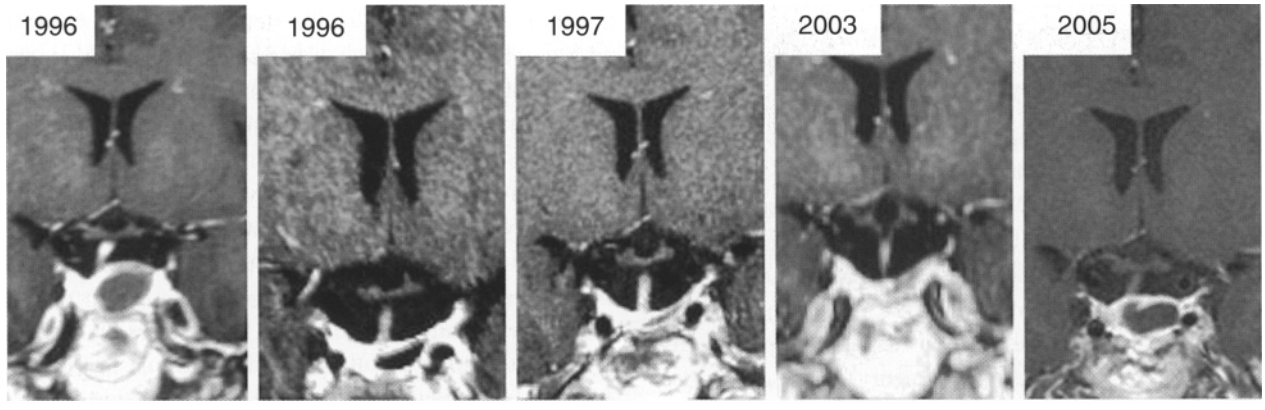

Fig. 3. Thirty six-year-old gentleman, with visual decline and headaches. Cystic craniopharyngioma recurred 1 year after transphenoidal complete removal. A stereotactic transphenoidal drainage of the cyst was followed by radiosurgery in 1996 (16 Gy to 70% isodoseline). Notice the control of the cyst for 9 years, when it recurred. Stereotactic radiotherapy was performed in 2005 (1.8 Gy to 90% isodose line, 28 fractions to a total of 50.40 Gy). The cyst has decreased in size and continues under control

cerebral spinal fluid are first managed with whole brain radiation therapy (WBRT), followed by imaging surveillance every three months. Radiosurgery is offered in case of new lesions or recurrence. This approach has avoided WBRT in 70% of the patients assuring better quality of life [2].

Low grade Gliomas are managed first with observation and SRT for cases with diffuse lesions or involving the optic apparatus. Discrete lesions are treated with SRS if possible. High grade Gliomas are preferably treated with regional conventional radiation therapy after a maximal resection. Stereotactic radiation is offered as a boost in selected cases [33]. Spinal lesions were treated with frameless stereotaxis and on line precision checks [8].

Discussion

Radiosurgery became an important addition on the armamentarium against trigeminal neuralgia [14]. Albeit powerful, it is the least invasive of the techniques [18, 19]. Using the protocol described above, 95% of the patients enjoy improvement of pain attacks. Recurrence is similar to the other techniques available, and a second treatment is possible, either with radiosurgery or any of the other techniques. Radiosurgery has the disadvantage of a latency period for pain response; therefore in cases of severe crises, the other techniques are preferred by our group [19]. Less successful applications of radiosurgery to control pain include sphenopalatine ganglinectomy [12], cingulotomy [13] and thalamotomy [15].

Epilepsy focus can be controlled by LINAC radiosurgery. Treatment of gelastic seizures caused by hypothalamic hamartomas has been successful to bring patients to a control at the level of Engle class II [31]. The senior author has a single experience on the treatment of left mesial temporal lobe seizure using the shaped beam approach with a dose of 17 Gy prescribed to the 90% IDL, 7cc volume. This patient had complete control of seizures, however need to use steroids for o period of 3 months due to radiation induced edema.

When possible, AVMs are managed with single dose application. Lesions larger than 5 cm in their largest diameter are managed in steps. Embolization is highly indicated in cases harboring large fistulas and aneurysms. These large fistulas do not respond appropriately to radiosurgery, and unsecured aneurysms pose high risk of bleeding.. The recanalization rate after embolization has been 9% in our earlier experience [27]. Therefore too early SRS following embolization may lead to failure to irradiate the recurrent portion of the AVM.

The acoustic neuroma treatment protocol evolved from single dose through hypofractionation schemes of 3 and 5 fractions. It was settled for 26 fractions of 2 Gy because of the outstanding results being observed with this protocol [11, 32]. Using 3 fractions of 7 Gy it was observed tumor swelling with need of steroid therapy. The scheme of 5 fractions led to the same hearing preservation of single dose when using from 12 to 14 Gy. Currently, the single dose of 12 Gy is used acoustic neuromas when there is no hearing to preserve.

Meningiomas involving the optic apparatus or with compression of the brainstem are treated with surgical decompression if possible, followed by either stereotactic radiosurgery or stereotactic radiotherapy. Deficits evoked by surgery are observed to resolution or stabilization to avoid a second insult to the structure in recovery. After surgery, depending on the meningiomas WHO classification [23], radiosurgery is deferred until confirmation of tumor recurrence. Patients are followed with imaging study in six-month intervals. When needed, the SRS or SRT choice for treatment depends on the need to avoid damage of structures involved by the tumor.

Radiosurgery took leading role on the management of metastases in our institution and many other advanced cancer centers. Our recent experience, currently under submission for publication by Ford *et al.* shows that when up to two intracranial lesions are present at the time of brain involvement, SRS offers statistically significant control rate and better quality of life than WBRT. Beyond two lesions significance was not found and WBRT must be entertained. Surgery should also be offered when possible for symptomatic lesions.

Gliomas either low or high grade are preferably managed by surgery, stereotactic radiation takes only an adjuvant role. Since focal radiation tends to lead to imaging changes of difficult interpretation when modern techniques are used, such as MRI, MRS or PET [17], we reserve stereotactic radiation only in the recurrent setting. This allows for better interpretation of results obtained with more promising clinical trials for these tumors, such as immunotherapy and chemotherapy.

The reduced time of treatment of complex radiosurgical lesions and the highly homogeneous dose to the lesion volume compares favorably to other radiosurgical techniques available and allow the choice of single, hypofractionation or full fractionated schemes. This provided increased effectiveness and decreased side effects, as demonstrated on the management of acoustic neuromas, cavernous sinus meningiomas and pituitary adenomas [28, 30, 32]. This experience has been transferred to

spinal radiosurgery where we have observed crude 100% control of benign lesions and 83% of malignant lesions using 12 Gy single dose. Using this dose, no radiation induced myelopathy has been observed [8].

Experiment work

Strategies of treatment and new applications have been based on animal experimentation including for functional radiosurgery [7, 37], vascular radiosurgery [9, 21, 22] and spinal radiosurgery [24].

Acknowledgments

The author acknowledges the participation of his current stereotactic radiation team as co-authors and previous team members in the reference list. Retrospective data evaluation has been permitted by the institutional review board.

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Acta Neurochir Suppl (2008) 101: 169–173

Printed in Austria

Hypofractionated CyberKnife stereotactic radiosurgery for acoustic neuromas with and without association to neurofibromatosis Type 2

D. T. Ju[1], J. W. Lin[2,3], M. S. Lin[2], L. M. Lee[4], H. M. Tseng[5], C. P. Wei[6], C. H. Yen[7], C. C. Hung[8], K. S. Hung[2], C. M. Lin[2,3], T. J. Lin[2], W. T. Chiu[2], J. T. Tsai[9,10]

[1] National Defense Medical Center, Department of Neurological Surgery, Tri-Service General Hospital, Taipei, Taiwan
[2] Department of Neurosurgery, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan
[3] Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[4] Department of Urology, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan
[5] Department of Neurosurgery, National Taiwan University Hospital, Taipei, Taiwan
[6] Department of Neurosurgery, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan
[7] Department of Neurosurgery, Far Eastern Memorial Hospital, Taipei, Taiwan
[8] Department of Neurosurgery, Taipei Medical University Hospital, Taipei, Taiwan
[9] Institute of Biomedical Engineering, National Yang-Ming University, Taipei, Taiwan
[10] Department of Radiation-Oncology, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan

Summary

CyberKnife stereotactic radiosurgery (CKSRS) has been proved effective in treating intra-cranial lesions. To treat acoustic neuroma (AN) patients with or without neurofibromatosis Type 2 (NF2) associations, the functional preservation of hearing, trigeminal nerve, and facial nerve are important.

Twenty-one patients were treated with hypofractionated CKSRS. Fourteen non-NF2 and seven NF2 patients were enrolled. Cranial nerve function, audiograms, and magnetic resonance images (MRI) were monitored.

Mean follow-up was 15 month. Tumors with volumes ranging from 0.13 to 24.8 cm^3 (mean 5.4 cm^3) were irradiated with the marginal dose 1800–2000 cGy/3 fractions. Tumors were treated with an 80 to 89% isodose line (mean 83%) and mean 97.9% tumor coverage. Two patients experienced hearing deterioration (16.7%) in the non-NF2 group, and 3 patients (50%) in the NF2 group. No facial or trigeminal dysfunction, brain stem toxicity, or cerebellar edema occurred. Tumor regression was seen in 9 patients (43%) and stable in 12 patients (57%). 100% tumor control rate was achieved.

Hypofractionated CKSRS was not only effective in tumor control but also excellent in hearing preservation for non-NF2 AN. But for NF2 patients, although the tumor control was remarkable, hearing preservation was modest as in non-NF2 patients.

Keywords: Acoustic neuroma; neurofibromatosis Type 2 (NF2); hypofraction; CyberKnife (CK); stereotactic radiosurgery.

Introduction

Acoustic neuroma (AN) is a slow-growing tumor, which occurs in adults with age ranging between 40 and 70 years. This tumor comprises 8–10% of intracranial tumor. Association with neurofibromatosis Type 2 (NF2) is seen in 2–4% [11]. NF2 typically presents with bilateral acoustic neuromas and mainly involves younger patients [18]. Whether non-NF2 or NF2 in type, AN always tends to infiltrate into, or compress on adjacent cranial nerves, such as the 5th, 7th and 8th cranial nerves. Treatment modalities available for AN, including surgical resection, stereotactic radiotherapy (SRT), and stereotactic radiosurgery (SRS) are aimed not only at controlling tumor volume but also at preserving function of adjacent cranial nerves [1, 8, 10, 14, 18]. Many publications report that surgical intervention for tumor resection always comes with high morbidity, such as hearing loss, facial nerve dysfunction, and brain stem insult [1, 6, 10, 16, 18]. However, SRT can provide only moderate tumor control, even though this treatment choice offers a better chance to preserve hearing function.

SRS has recently been proved effective for tumor control and functional preservation in patients with ANs [1, 7, 8]. Published radiobiological articles show that single-stage radiosurgery can control the tumor quite well but hearing can be maintained in only 50–73% of the AN patients [1, 7, 17]. In comparison, hypofractionated treatment modality, such as CyberKnife (CK) therapy, can mitigate cranial nerve deterioration [20]. By delivering a few fractions of smaller radiation doses, CK

Correspondence: Jo-Ting Tsai, M.D., Department of Radiation-Oncology, Taipei Medical University-Wan-Fang Medical Center, Institute of Biomedical Engineering, National Yang-Ming University; 111, Section 3, Hsing-Long Road, Taipei, Taiwan. e-mail: kitty@wanfang.gov.tw

SRS can provide 74 to 78% hearing preservation for non-NF2 patient [1]. However, for NF2 patients with AN, the hearing preservation is not as ideal as for patients with non-NF2 AN. In this study, we applied CK SRS to the treatment of non-NF2 and NF2 patients with ANs and analyzed the therapeutic results and side effects of this treatment modality in both the non-NF2 and NF2 groups.

Materials and methods

Patients

From 2005 September to 2007 October, 21 patients with ANs (13 right: 8 left) were treated. Among them, 7 patients were diagnosed to have NF2, and images showed bilateral ANs in 6 patients. For the 6 NF2 patients with bilateral ANs, only one target with the major symptom was treated in this period of time. One patient had had surgical treatment before and the tumor recurrence was identified during the follow-up period, and the other 20 patients received CKSRS as the primary treatment. Eleven patients were females (55%) and 10 patients (45%) were males. The mean age was 54 years (range: 27 to 79 yrs). Tumor volume ranged from 0.13 to 24.8 cm^3 (mean 5.4 cm^3). The post-treatment follow-up duration for these 21 patients ranged from 6 to 25 months (mean: 15 months). Basic patient information is listed in Table 1.

Table 1. *Patients' clinical data*

Number of patients	21
Male	10
Female	11
Mean age (year)	54 (range: 27–79)
Association with NF-2	7
non NF-2	14
Mean follow up time (months)	15 (range: 6–25)
Mean tumor volume (cm^3)	5.4 (range: 0.13–24.8)
Prescribed marginal dose (cGy)	1800–2000
Fractions	3
Mean isodose (%)	83 (range: 83–89)
Coverage (%)	97.9 (range: 94.8–99.4)
CI	1.27 (range: 1.14–1.59)
HI	1.19 (range: 1.12–1.27)
NCI	1.38 (range: 1.16–1.67)

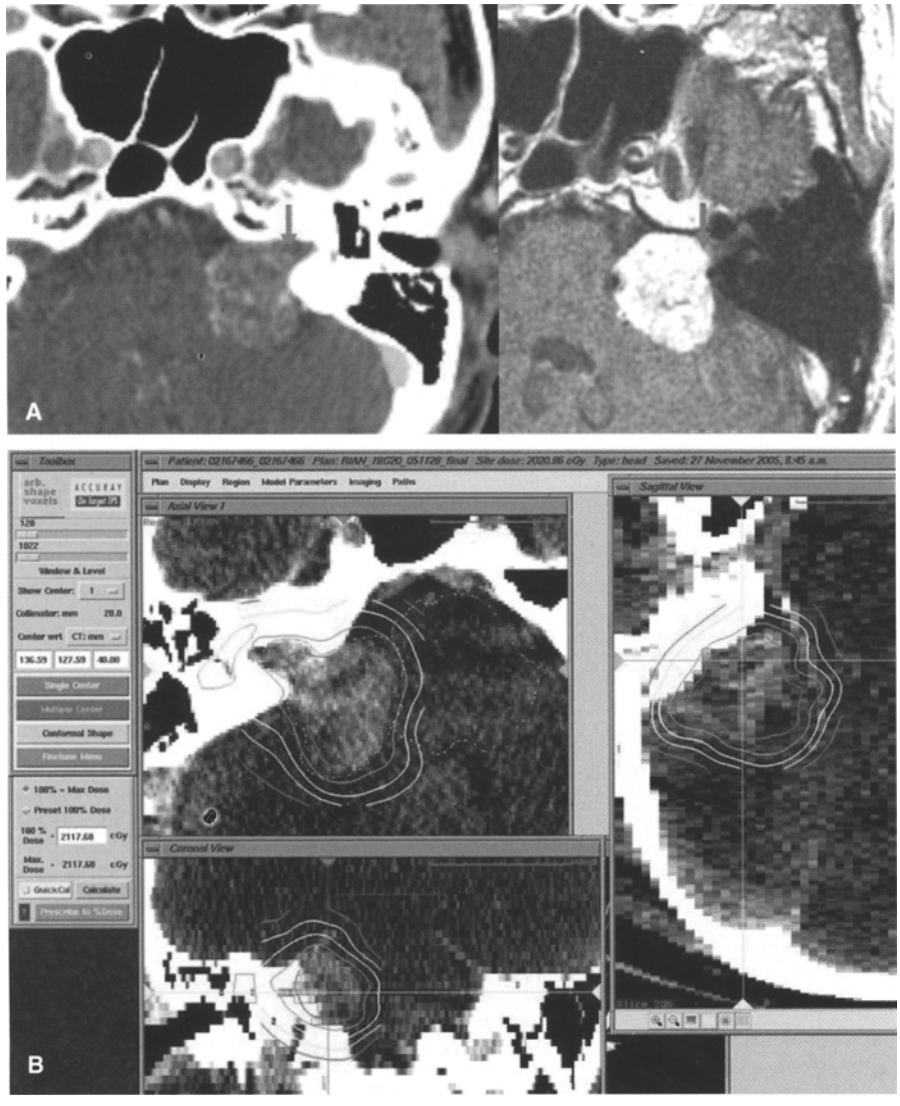

Fig. 1. (A) Comparison of contrast-enhanced axial CT scans (*left*) with enhanced T1W MRI (*right*) of same patient harboring acoustic neuroma with intra-canacular extension. MRI was superior in identification of tumor margin in IAC (*arrow*), facilitating protection of vital organs, such as cochlear, in IAC from irradiation. (B) Non-isocentric inverse planning: no hot or cold spot could be identified; isodose line runs along adjacent border between tumor and brain stem ideally for irradiation delivery

Clinical evaluation

All the patients were evaluated routinely with neurological examination, audiogram, and MRI, which were taken as a baseline reference. Hearing and functions of the facial trigeminal nerves were graded according to the Gardner-Robertson classification system (GR), House-Brackmann grading system (HB), and semi-quantitative scale [1]. MRI T1W image with enhancement was used to evaluate the tumor size, and T2 flair image was used to evaluate perifocal edema of the brain stem and cerebellum before and after the CKSRS. Among 7 AN patients associated with NF2, the major symptoms before CKSRS were hearing impairment ($n=7$; 100%) and tinnitus ($n=6$; 86%). As to the patients without NF2, the following manifestations were seen in some: trigeminal neuralgia ($n=1$; 7.1%), facial palsy ($n=3$; 21.4%), tinnitus ($n=11$; 78.6%), and hearing impairment ($n=13$; 92.9%). After the CKSRS, all above image studies and clinical evaluation were repeated 3, 6, 12, 18, and 24 months after the treatment.

Tumor size measurement

Tumors shown in MRI were measured in three orthogonal dimensions. Tumor volume (Vol) was calculated as: Vol (mm^3) $= \pi (a \times b \times c)/6$, where a, b, and c represent width, height, and thickness, respectively [13]. For each patient, the last follow-up MRI was compared with MRI before treatment [1].

Image fusion, tumor delineation, and treatment planning

Thin-sliced (1.25 mm) high-resolution CT images were obtained for tumor delineation after intravenous administration of 125 ml of Omnipaque contrast (iohexol, 350 mg I/ml; Nycomed Inc., Princeton, NJ). If the tumor involved the internal auditory canal (IAC) and IAC dilatation was confirmed, MRI image was then arranged for image fusion in order to prevent an unnecessary dose on CNVII and CNVIII in the IAC (Fig 1A).

A conformal inverse planning method with non-isocenteric technique was used for all cases (Fig 1B). The treatments for all patients were given with 3 equal dose fractions. The total dose was 18 Gy for patients with hearing GR1–4 to reduce the risk of hearing impairment. For patients with hearing GR5 before the SRS, we prescribed 20 Gy for better tumor control. All planning was evaluated with dosimetry indices for optimal results, including tumor coverage percentage, homogeneity index (HI), conformality index (CI), and new conformality index (NCI). The data for these indices are summarized in Table 1.

Results

Tumor response on MRI image

During an average of 15-month follow-up, there was no patient who suffered from tumor recurrence. For the

Table 2. *Tumor control after CKSRS*

	Stable	Regression	Total	
Non-NF2	7 (50.0%)	7 (50.0%)	14 (100.0%)	
NF2	5 (71.4%)	2 (28.6%)	7 (100.0%)	
Total	12 (57.1%)	9 (42.9%)	21 (100.0%)	OR = 2.5

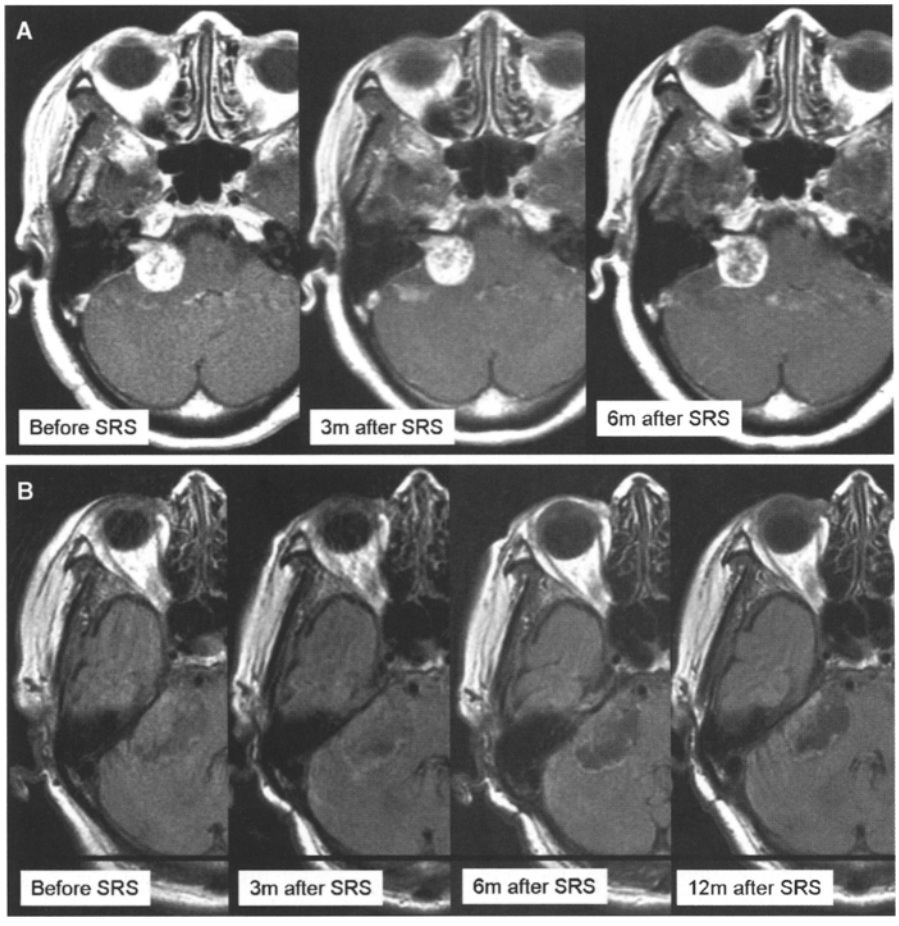

Fig. 2. (A) Series Gd-enhanced T1W MRI: gradually loss of central enhancement 6 months after CK SRS. (B) Series T2W flair image for 12 months follow up: no evidence of new perifocal edema around brain stem or cerebellum even though tumor diameter was around 4.2 cm in diameter

Table 3. *Hearing preservation after CKSRS*

	Deterioration	Preserved	Total	
Non-NF2*	2 (16.7%)	10 (83.3%)#	12 (100.0%)	
NF2$	3 (50.0%)	3 (50.0%)	6 (100.0%)	
Total	5 (27.8%)	13 (72.2%)	18 (100.0%)	OR = 5.0

* Two patients excluded from non-NF2 group and $1 patient excluded from NF2 group because of GR5 hearing.
# One patient in non-NF2 group not only preserved but also got some improvement about the hearing function (from GR3 to GR2).

NF2 patient, 5 tumors (71.4%) were under stable condition and 2 patients (28.6%) had tumor regression. Among the non-NF2 patients, 7 tumors (50%) were stable and 7 tumors (50%) shrunk (Table 2). The response in non-NF2 patients seems better than in NF2 patients (OR = 2.5).

Loss of enhancement inside the tumor was observed on MRI images 6 months after the SRS (Fig. 2A), and there was no correlation with tumor regression. For all the patients followed up for more than 1 year, the series of MRI T2 flair images showed no evidence of perifocal edema within the adjacent brain stem or cerebellum (Fig. 2B).

Preservation and improvement of cranial nerve functions

Hearing in non-NF2

For the 14 non-NF-2 patients, 2 patients did not have detectable hearing (GR5) and were excluded. The remaining 12 patients had GR1 to 4 hearing before treatment. Two patients showed hearing deterioration, from GR2 to 3 in one and from GR3 to 4 in the other. The remaining 10 patients preserved their original hearing after the SRS (83.3%). One of these 10 patients even showed improvement from GR3 to GR2 (Table 3).

Hearing in NF2

For the 7 patients associated with NF-2, 1 patient had hearing impairment with GR5 before treatment. Three of other 6 patients with hearing GR1 to 4 (50%) retained their hearing at the last follow-up. None showed improvement in the follow-up period. Our results are comparable with those in the currently papers, which show an average of 40–50% of hearing preservation in NF-2 patients [5, 11, 18] (Table 3).

Trigeminal and facial nerve

One patient suffering from trigeminal neuralgia before treatment had improvement with decreased pain frequency and intensity (from VAS 9 to 3 without medication). Three patients with facial palsy (House-Brackmann grading 2 before treatment) kept the same condition without any deterioration after the SRS. No new facial and trigeminal dysfunction developed in any patients. No patients experienced brain stem toxicity or cerebellar edema.

Discussion

Nowadays, the management of AN has been well established. Available strategies of ANs include surgery and non-surgical treatment, such as SRT and SRS. In some instances, a larger tumor causes prominent compression on the brain stem or cerebellum and an invasive treatment procedure for decompression, such as microsurgery, is still needed. However, many publications have reported significant morbidity of microsurgery, which includes cranial nerve dysfunction [9, 16] and low hearing preservation (50–60% overall, decreased to 16% if the tumor size is larger than 1.5 cm) [1, 14, 15]. Therefore, non-invasive treatment, such as SRS, has become an alternative option for ANs.

Single staged SRS has proved to have high conformality, and its tumor-control rate reaches about 95%, with 50–73% hearing preservation after long term follow-up [7, 15, 17, 19]. Such a result is not good enough for a functional preservation-oriented treatment option. Hypofractionated CKSRS is theoretically and clinically proved to be effective in reducing irradiation damage to normal vital structures and producing significant hearing preservation in AN treatment [1, 2, 4, 14]. Furthermore, if AN is treated with single fraction SRS and the tumor size is larger than 3 cm or the tumor volume more than 27 ml, there may be some delayed radiation effect on the adjacent structure [1]. Not only tumor swelling but also perifocal edema will compress on the brain stem and result in severe adverse neurological deficits. But in our experience there was no such rigid limitation for CKSRS. In Fig. 2B, there is no evidence of new-onset perifocal edema around the AN during the 12-month follow-up period, though the tumor was large (4.2 cm in longest diameter). Clinically there was also no brain stem toxicity or cerebellar edema in our 2-year experience.

Our report would strongly support that hypofractionated CKSRS provides an ideal tumor control rate, as in other single-staged SRS systems. In our small series and limited follow up duration (mean 15 m), a 100% control rate was achieved (42.9% regression and 57.1% stationary). Furthermore, with regard to hearing protection, our results were comparable with those from other larger series: 72.2% for overall and 83.3% and 50% for non-

NF-2 and NF-2 patients, respectively. We prescribed the marginal dose for 18–20 Gy/3 fractions, and this hypofractionated dose is equivalent equal to 12, 13 Gy/single fraction ($\alpha/\beta = 2$ Gy). According to previous reports, using single-stage dose of less than 14 Gy can retain 71–73% of useful hearing. This may also explain the low risk for hearing impairment [1].

For the CKSRS system, all the tumor delineation and treatment planning were based on the CT scan images. If the tumors have involved the IAC and the IAC is enlarged by the tumor invasion, then MRI with enhancement has higher sensitivity than an enhanced CT scan on identifying the real tumor contour, cranial nerve, and IAC [3]. Fused image with MRI will then be necessary.

Data of our dosimetry indices, 97.9% tumor coverage, 1.3 mean CI, 1.2 mean HI, and 1.4 mean NCI, have demonstrated ideal conformality, homogeneity, and accuracy, which may be the basis of hearing preservation. Two of patients in the non-NF2 group suffered from hearing deterioration, and both the CI and NCI for these two patients were larger than 1.5. This might be the reason why the patients could not keep their original hearing function.

Finally, AN is a complex disease and it can be present with both the sporadic AN and genetically transmitted pattern (NF2, chromosome 22 abnormality) [11, 18]. ANs associated with NF2 tend to involve the cochlear nerve more invasively, and result in significant hearing impairment [12, 18]. The outcome of SRS treatment on NF2 patients is also undesirable, with only around 50% of hearing preservation [11, 18]. In our result present series, only 50% of NF2 patients preserved original hearing function. This result was not superior that in other single-staged SRS systems.

As almost all the SRS can achieve a very good tumor control rate (more than 95%), the choice for different SRS systems should rely on the ability of hearing preservation and lesser toxicity to the brain stem and cerebellum. Our 2-year experience strongly suggests that hypofractionated SRS be an ideal modality to provide excellent hearing preservation and adjacent vital nerve protection for ANs.

Acknowledgements

The authors would like to acknowledge the grant from the Department of Health, Executive Yuan, Taiwan (DOH-TD-B-111-002), the grant (NHRI-EX97-9707PI, NHRI-CN-HD9503S) from National Health Research Institute, Taiwan, the grant (NSC 96-2314-B-038-010-MY2) from National Science Council, Taiwan, and the grant (96001-62-010) from Department of Health, Taipei, Taiwan.

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