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ORIGINAL ARTICLE

Management of intrathecal baclofen therapy for severe acquired brain injury: consensus and recommendations for good clinical practice

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Abstract Although widespread in the treatment of generalised spasticity due to severe acquired brain injury, clinical use of intrathecal baclofen administered through an implanted catheter is not yet supported by full scientific evidence. The aim of the study is to provide recommendations for good clinical practice regarding intrathecal baclofen therapy. We used a modified RAND Delphi method to develop consensus-based medical guidelines, involving clinicians who use intrathecal baclofen therapy throughout Italy. The clinicians were asked 38 questions grouped in six areas (patient selection, contraindications for implant, tests prior to implant, method of implant and management of therapy, efficacy evaluation and goal setting, and management of complications). To establish consensus, 75% agreement was required in answers to every question. Consensus was reached on the second round of the Delphi process on 27/38 questions (71%), specifically those regarding identification of objectives, efficacy evaluation, and method of implant and management of therapy, whereas management of complications and contraindications for implant remained critical areas. Despite the limits of our method, a set of recommendations was drawn up for clinical practice in this sector. The study also revealed residual critical areas and indicated future lines of research necessary to reach evidence-based consensus.

Keywords Severe acquired brain injury · Spasticity · Intrathecal baclofen · Rehabilitation

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Introduction

Many survivors of severe brain injury (sABI) have significant symptoms for many years. Consequences can include disorders of consciousness (DoC), pain, disorders of balance, cognitive impairment, difficulty walking or using upper limbs, and dependence on wheelchair. Although rehabilitation can promote recovery after brain injury, symptoms persisting after acute and post-acute phases can lead to functional limitation, dependence on others for activities of daily living, and delayed return to work or school [1]. Severe spastic hypertonia can be the most disabling of the many consequences [2]. It may interfere with transfer activities, make wheelchair activity almost impossible, promote bedsores, and mask or prevent residual motor activity so that contractures develop, making nursing, personal care, and movement difficult [3, 4]. A comprehensive stepwise approach to spasticity seems to be the most appropriate method of treatment and many algorithms have been formulated.

Chemodenervation with botulinum toxin type A or phenol neurolysis may be used, especially in cases of focal spasticity, but the utility of botulinum toxin in multisegmental involvement is limited and neurolysis may be associated with adverse events, such as dysaesthesia and oedema [5]. Surgical procedures, for example peripheral nerve surgery, are used in very select cases [6]. Oral spasmolytic drugs include tizanidine, baclofen, and dantrolene. Baclofen is a gamma-aminobutyric acid ($GABA_B$) receptor agonist [7] used worldwide. However, even at recommended doses (≤75 mg/day), oral baclofen can cause side effects such as sedation and mental confusion or may have little effect on hypertonia. Intrathecal baclofen (ITB) delivered by an implanted catheter allows a higher concentration of the drug to reach the sensorimotor pathways of the spinal cord, reducing spasticity through presynaptic inhibition. ITB requires only a small dose of baclofen to exert its effects on the spinal neurons. In fact, a mean plasma-to-cerebrospinal fluid concentration ratio in the range 8:1 to 100:1 is reported [8]. The catheter tip is usually placed at T11–T12, but other studies report that placement at T6–T7 or T2–T4 provides greater relief of upper extremity spasticity without loss of effect on the lower limbs [4]. Since the work of Penn and Kroin several decades ago [9], the efficacy of ITB in the management of spasticity due to spinal cord injury, cerebral palsy, stroke, and multiple sclerosis has been reported in many papers [3, 10–13]. Francisco [14] showed that ITB treatment in patients with traumatic brain injury (TBI) brought improvements in mobility, personal hygiene, and participation in daily activities; moreover, therapy did not appear to adversely affect functional outcome. Schiess reported that 12 months of ITB therapy enabled most patients to achieve greater participation and interaction as well as significant improvement in mobility, upper limb function, and self-care [4].

In another study, ITB proved useful in the control of episodes of paroxysmal dysautonomia (PSH) [15]. A few case reports observed an effect of ITB on DoC recovery [16]. Negative aspects of ITB include repeated visits to refill the pump and to adjust the level of infusion, infections, and technical complications after pump placement (battery failure, tube disconnection, erosion of pump, occlusion, breakage, or disconnection of the catheter) [17]. Proper patient selection and meticulous attention to surgical technique ensure a low risk of infection.

Although ITB is effective in reducing hypertonia and improving functional abilities, several aspects still have to be discussed with regard to sABI. For example, there is currently no consensus among clinicians regarding the outcome measures to use in practice [18], the timing of pump implantation [6, 19], and whether to programme the pump to deliver medication at a constant or variable rate [8]. These differences limit the possibility of comparing and communicating data between centres, patients, and studies. Against this background, we present the results of an Italian consensus process aimed at defining good clinical practice recommendations for ITB in the treatment of generalised spasticity in adults with sABI.

Methods

Consensus group formation

In June 2014, a group of eight Italian clinicians with more than 15 years of experience in the treatment of generalised spasticity in patients with sABI formed a steering committee (SC). A working group (WG) was then formed by invitation of the SC, based on clinical or research experience with the condition, clinical specialities (neurology and rehabilitation medicine), and geographic location in Italy. Of the 63 experts invited as panellists, 41 contributed answers. However, for the purposes of the consensus process, only the answers of the 30 clinicians (47.6%) who completed both rounds were considered. WG members had a mean experience with ITB of 10.6 years (2–30).

Consensus process

The SC selected a modified RAND Delphi method to develop consensus-based medical guidelines. Typically, a Delphi procedure consists of a written round and a face-to-face round [20]. It is a widely used and accepted procedure for achieving convergence of opinions concerning real-world knowledge. Answers are solicited from experts in certain topic areas when there is insufficient scientific evidence on which to base recommendations for good clinical practice. Average scores are fed back to the group for a second round, to give respondents the opportunity to revise their scores in the light of group perceptions; consensus is often reached in the second round of the process [21]. In our case, communication occurred via email and document sharing rather than by personal meeting or telephone. This minimised bias due to excessive influence of individuals with strong personality types and political/academic stature [22].

Activation of the consensus process was preceded by a systematic search of the English literature in PubMed using search terms such as general hypertonia, intrathecal baclofen therapy, and brain injury, combined with "AND/OR" assessment, therapy, and management. Afterwards, a list of questions was presented to the members of the WG.

The SC decided on a 95% confidence interval (CI) for the degree of uncertainty associated with each response frequency in order to obtain an interval estimate combined with a probability statement. We arbitrarily established that agreement on the answer greater than or equal to 75% (57.3–87.025 95% CI) was acceptable since the lower limit was above 50%.

The consensus process was developed in two rounds. In the first round, the WG was invited to respond to a 30-question survey. This round included multiple-choice questions (21) and yes/no answers (9), but all questions had a free field where participants could actively propose solutions not originally foreseen by the SC. By this procedure, the 75% agreement threshold was only reached for 5/30 questions at the end of the first round, but analysis of the responses made it possible to propose a second round with 38 questions. At least 75% agreement was reached on 27/38 (71.05%) of the answers. After comprehensive analysis of the responses, the SC took note of the lack of consensus on 11 questions and did not consider it necessary to organise a third round.

Results

The list of 38 questions in the final re-elaboration of the questionnaire and the answers with the highest consensus to each question is available on the website http://ITB.sstefano.it

Twenty-seven answers with agreement reached in more than 75% of participants (Table 1) were adopted as:

1. *Patient selection*. Agreement was reached on the use of three International Classification of Functioning, Disability, and Health (ICF) domains (body functions, activity, and participation) for evaluating the possibility of implanting an ITB pump in patients with generalised spasticity, and the expedience of defining a primary as well as secondary objectives. Appropriate objectives were considered to be reduction of care burden and easier nursing, prevention of structural deformities, improved wheelchair posture, easier management of daily and social life, easier physiotherapy programme, combatting PSH, and facilitating renewed contact with surroundings.
2. *Contraindications for implant*. Active infections and life expectancy less than 6 months were considered absolute contraindications for ITB implant.
3. *ITB screening test*. Consensus was reached on the recommendation to check the efficacy and possible side effects of oral muscle relaxants, in particular baclofen, before considering intrathecal administration. The recommendation to always perform an intrathecal administration test with the drug before any pump implant was also adopted.
4. *Implant method and management of therapy*. Agreement was reached to reject the hypothesis that the initial dose of baclofen after pump implant should be double the test dose and that at least 3 months should elapse after the acute event before pump implant. In the management of ITB therapy, check-ups with a predefined period are recommended, as is considering modified modes of infusion to optimise the efficacy of therapy.
5. *Efficacy evaluation and goal setting*. The panellists were in broad agreement on most of the measurement tools proposed by the SC: the Ashworth [23] and/or Tardieu scale [24] to assess muscle tone; Penn scale for spasms [25]; NCS-R (Nociceptive Coma Scale-Revised) [26] for pain in DoC; a digital scale such as VAS (Visual Analogic Scale) or NRS (Numeric Rating Scale) for pain in responsive patients; the MRC (Medical Research Council) scale [27] to measure force; the Trunk Control Test for posture [28]; the Paroxysmal Sympathetic Hyperactivity assessment measure (PSH-AM) to assess control of PSH [22]; the CRS-R (Coma Recovery Scale-Revised) [29] for assessment of consciousness; and FAC (Functional Ambulation Categories), the 6-min or 10-m walking test [30] to assess walking.
6. *Management of complications*. It did not prove possible to formulate recommendations in this area.

In the following cases, the 75% consensus threshold was not reached:

1. *Patient selection*. Agreement was not reached on the Goal Attainment Scale (GAS) [31] for identifying objectives and assessing their achievement.
2. *Contraindications for implant*. Agreement was not reached on incompatibility of implant in cases of multiple muscle-tendon retractions, major skin lesions, and cardiovascular instability.
3. *ITB screening test*. There was no consensus that preliminary assessment should be done with a single dose.
4. *Implant method and management of therapy*. The consensus threshold was not reached for the statement that the initial dose after the "infusion" test should be the same as the optimal dose in the preliminary test, that the simple infusion mode is the most effective, and that in the case of generalised spasticity, ITB therapy should always be considered before functional surgery.
5. *Efficacy evaluation and goal setting*. The consensus threshold was not reached for the two questions regarding the best test to assess efficacy in terms of upper limb and the best test to assess efficacy in terms of overall evaluation. In the first case, the Nine-Hole Test was preferred; in the second, the proposal to use FIM + FAM was preferred to the Barthel Index.
6. *Management of complications*. Regarding the best approach to seizures in patients with ITB, reducing the dose of baclofen and establishing antiepileptic therapy were preferred to alternative solutions involving reducing baclofen dose alone and beginning antiepileptic therapy alone. Regarding the approach to infection at the pump site, targeted antibiotic therapy was preferred to immediate explant of the device or explant only in the case of documented meningitis.

Table 1 Answers with agreement reached in more than 75% of participants

Question	Percent
Patient selection	
-In assessing the possibility of implanting an intrathecal baclofen pump, I think it is appropriate to classify problems derived from generalised spasticity in terms of... "Functions, activities and participation"	92.85
-Do you think it is important to define a primary objective and secondary objectives? [Choose only one answer]	87.7
-Do you think that *reduction of paroxysmal sympathetic hyperactivity* can be a primary or secondary objective of implant of an ITB pump in patients with SGS?	88.4
-Do you think that *facilitating renewed contact with surroundings* can be a primary or secondary objective of implant of an ITB pump in patients with SGS?	84.6
-Do you think that *prevention of structural deformities* can be a primary or secondary objective of implant of an ITB pump in patients with SGS?	96.4
-Do you think that *reduction of care burden and easier nursing* can be a primary or secondary objective of implant of an ITB pump in patients with SGS?	100
-Do you think that *wheelchair posture* can be a primary or secondary objective of implant of an ITB pump in patients with SGS?	96.4
-Do you think that *an easier physiotherapy programme* can be a primary or secondary objective of implant of an ITB pump in patients with SGS?	92.8
-Do you think that *easier management of daily and social life* can be a primary or secondary objective of implant of an ITB pump in patients with SGS?	96.4
Contraindications for implant	
-Do you think that a *life expectancy of less than 6 months* is an absolute contraindication for implant of an intrathecal infusion system?	75
-Do you think that *infection* is an absolute contraindication for implant of an intrathecal infusion system?	82.1
ITB screening test	
-With reference to the screening test, do you think it always necessary to do a preliminary test?	89.28
-Do you think it necessary to first test oral muscle relaxants (including baclofen)?	82.1
Implant method and management of therapy	
-Do you think that after a single-dose test, the starting dose should be double the test dose?	77.7
-Apart from technical criteria, do you think it is necessary to wait at least 3 months after the acute event before undertaking implant of an ITB infusion pump?	75
-In the management of ITB therapy, do you think it necessary to conduct check-ups at predefined intervals?	89.2
-Do you think it useful to modify infusion mode to improve the effect of ITB therapy?	100
Efficacy evaluation and goal setting	
-To measure efficacy in terms of *muscle tone,* do you think that the Ashworth and/or Tardieu scale is the best choice?	92.8
-To measure efficacy in terms of *spasms,* do you think that the Penn scale is the best choice? (Please answer even if your answer to the previous question was no)	89.2
-To measure efficacy in terms of *pain in unresponsive patients,* do you think that the -NCS-R (Nociceptive Coma Scale – Revised) is the best choice?	78.2
-To measure efficacy in terms of *pain in responsive patients,* do you think that a digital scale (e.g. VAS (Visual Analogic Scale) or NRS (Numeric Rating Scale)) is the best choice?	96.2
-To measure efficacy in terms of *force,* do you think that the MRC (Medical Research Council) scale is the best choice?	85.7
To measure efficacy in terms of *posture,* do you think that the Trunk Control Test is the best choice?	85.18
-To measure efficacy in terms of *vegetative system,* do you think that the Baguley Consensus is the best choice?	90.47
-To measure efficacy in terms of *level of consciousness,* do you think that the CRS-R (Coma Recovery Scale – Revised) is the best choice?	100
-To assess *walking function,* do you think that FAC (Functional Ambulation Categories) are sufficient?	77.7
-To assess *high-functional walking performance,* do you think that the 6-min and/ or 10-m test are sufficient? (Please answer even if your answer to the previous question was no)	82.1

SGS severe generalised spasticity

Discussion

A high degree of agreement about the utility of the conceptual model provided by ICF to frame overall analysis of the rehabilitative needs that can be met by ITB therapy emerges from the answers of the experts. This made it possible not only to focus their attention on the immediate objective of reducing spasticity but also to always bear in mind functional objectives aimed at improving activity and participation with a final effect on quality of life. This facilitates a more analytical definition of the objectives proposed by the rehabilitation team, as well as communication of these objectives to patients and their caregivers [32]. Though with slightly less consensus than for other questions, the WG also recommends ITB therapy to facilitate recovery of consciousness. On this topic, the literature is less solid, consisting of case reports and small case series [15, 33]. The experts sustain that promoting recovery of consciousness is mediated by a reduction in generalised spasticity that blocks the experience of movement and interaction with surroundings, but also because baclofen blocks an overload of dysfunctional sensory stimuli reaching the injured brain or by stabilising unbalanced circadian rhythms [34]. Pain reduction and the effect of baclofen in reducing episodes of PSH are also considered elements that favour improvement of consciousness after sABI [35].

In the "patient selection" domain, the threshold consensus was not reached on the GAS as an optimal tool for establishing objectives, priorities, and results. In our opinion, it would be useful to conduct a study to determine optimal use of GAS, which has the advantage of being flexible but must be applied rigorously and tailored to experimental protocols to increase its reliability and validity as a research measurement tool [36]. With regard to "contraindications for implant", the SC takes note that consensus was not reached in judging cardiovascular instability and haematological problems as possible exclusion criteria for implant of ITB, probably because their severity and invariance were not sufficiently specified in order to consider them absolute exclusion criteria for implant. Lack of consensus on the question of skin lesions is also considered legitimate and it is recommended that the final decision regarding implant be entrusted case by case to a group of specialists, in relation to lesion extent and site. Likewise, it was agreed that multiple muscle-tendon retractions are not absolute contraindications for ITB implant, which could be aimed at limiting deterioration or one of the other possible objectives indicated in the previous section. With regard to "ITB screening tests", the WG determined to recommend a screening test that assesses response to a test dose of ITB on spasticity and function and identifies adverse reactions after checking the utility and possible side effects of therapy with oral muscle relaxants [37]. The Steering Committee considers it correct to reject the hypothesis of always using a single-dose test and favours research to define under what conditions a single-dose test is most indicated and when a continuous baclofen infusion test (by portable external pump and intrathecal catheter with daily dose adjusted according to clinical response) is more informative. This method offers the possibility of a longer observation period and could be useful for assessing the efficacy of the drug in favouring recovery of consciousness [33] or the possibility of improving walking where it is necessary to titre the drug to balance the reduction in spasticity with the risk of excessive weakness.

In the domain of "implant method and management of therapy", the consensus threshold was achieved for the statement that implant can be considered if 3 months have elapsed since the acute event, which becomes a recommendation. This question is also widely debated in the literature; it seems likely that by increasing experience and reliability of this procedure, it has become possible to progressively bring forward the indication for its use, with the advantage of preventing the secondary effects of spasticity and the risk of a chronic condition. In 2005, Francisco [3] reported a case series in which "early" implant was within 1 year of the acute event, whereas in 2015, Posteraro [19] considers implant within 6 months of the acute event to be "early". The panellists were not sufficiently in agreement about the statement that "simple continuous mode", although the most frequently used, is the best mode of infusion. A study to determine categories of patients in whom other modes of administration, such as variable 24-h flex dosing or regularly scheduled single doses [38], is considered necessary. With regard to "efficacy evaluation and goal setting", all the single measures of efficacy proposed were agreed with high consensus; all the scales are widely validated and used in clinical practice and research, so that their standard use is recommended for routine assessment of patients under ITB therapy. Not surprisingly, consensus was not reached for identification of a single scale to summarise the results achieved (proposals were FIM + FAM and BIM). The complexity of these patients and the great number of factors that can determine outcome make their reduction to a single index rather questionable. Regarding analysis of the consensus results, the SC suggests to combine "objective" assessment scales with a tool that records patient and caregiver acceptance.

With regard to "management of complications", because of the composition of the WG, only medical complications were analysed and not those associated with the surgical implant procedure. Sufficient agreement was reached to recommend beginning and increasing antiepileptic therapy in the case of seizures concomitant with the start of ITB therapy, but the panellists were divided about the need for simultaneous reduction/suspension of baclofen infusion. The topic calls for further study because the literature only describes anecdotal cases [39] and recommends epilepsy prevention in patients with sABI treated with ITB [40] whereas data on incidence and risk analysis is needed. The different orientation of the

answers is probably also affected by the different emergency cover provided by different organisational models of Italian rehabilitation units: it is one thing to manage ITB in a complex hospital with all emergency services and quite another to operate in rehabilitation centres lacking, for example, intensive care.

Study limitations

Our study shows some limits which are well known as possible disadvantages of the Delphi technique:

1. Judgments are those of a select group of people and may not be representative [41].
2. Our panel included representatives from a close range of disciplines, neurology or physical and rehabilitative medicine. It is possible that somewhat different conclusions might be reached if there had been a higher proportion of representatives of other disciplines, such as surgeons or anaesthetists.
3. Tendency to eliminate extreme positions and force a middle-of-the-road consensus: the Delphi method has also been criticised for lacking standards for determining who was an expert [42], lacking a common starting point that provided panellists with current assumptions and findings, facilitating conformity rather than consensus, promoting quick answers to complex problems, and suppressing divergent views [43].
4. Another disadvantage of Delphi is a potentially high attrition rate. Because the method requires lengthy responses in the rounds of the process and the active participation of panellists over several months, the potential for a high drop-out rate of panellists exists.

We conclude by arguing that Delphi is not a quantitative method to reach an absolutely neutral answer to controversial issues but a technique to facilitate deliberation on a problem and to aggregate the informed opinions of experts in clinical problems with a lack of evidence [21].

Conclusions

The authors are aware that the results of their research cannot be considered guidelines for medical practice because they are not completely based on comparable evidence-based data but only on expert opinion. Nevertheless, they sustain that the results of the consensus conference make a significant contribution to the definition of an agreed therapeutic procedure for ITB in patients with sABI, based on collection of available evidence from the literature combined with expert opinions obtained by a formal transparent consensus method, as defined by a modified RAND Delphi method. This procedure made it possible to pinpoint grey areas where agreement is insufficient and on which it will be necessary to create prospective multicentric studies with direct involvement of other specialists, especially those responsible for the implant phase, who in Italy are mainly neurosurgeons, anaesthetists, and pain therapists.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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