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R. Becker
O. Alberti
B. L. Bauer

Continuous intrathecal baclofen infusion in severe spasticity after traumatic or hypoxic brain injury

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R. Becker (✉) · O. Alberti · B. L. Bauer
Department of Neurosurgery,
Philipps University Hospital,
Baldingerstrasse,
D-35033 Marburg, Germany
Tel.: (06421) 283238,
Fax: (06421) 285751

Abstract Severe spinal spasticity has been shown to be a good indication for continuous intrathecal baclofen infusion (CIBI), but there is only limited experience with this treatment in patients with supraspinal spasticity. Eighteen patients with severe spasticity from traumatic or hypoxic brain injury were treated with CIBI. In all patients spasticity could be reduced significantly. The mean Ashworth score was reduced from 4.5 to 2.33 and the mean Spasm frequency score from 2.16 to 0.94. This reduction of spasticity led to a marked pain reduction. Nursing, perineal care and mobilization became much easier. The complication rate was low. In this series we saw one infection in the pump pocket, one epileptic seizure after a bolus application of baclofen and one spinal catheter displacement. The results are similar to those reported from series of patients with spinal spasticity and correspond to the limited experience we have so far with supraspinal spasticity patients. To prevent limb contractures CIBI should be performed as soon as the patient is in a stable clinical condition after brain injury. Further prospective clinical trials will be necessary to obtain more experience with patients suffering from supraspinal spasticity.

Key words Intrathecal infusion · Baclofen · Supraspinal spasticity · Cerebral palsy · Implantable pump

Introduction

Spasticity of either spinal or supraspinal origin may compromise patients severely and is associated with the development of pain, limb contractures and immobility. Until 1984 therapeutic options were restricted to destructive surgical procedures, such as selective posterior rhizotomy [20], peripheral nerve blocks and neurotomies [13, 14] or oral medication with antispastic agents such as baclofen, dantrolene, tizanidine or diazepam [5]. Baclofen is a structural GABA analogue substance acting at the GABA-B receptor subtype. It is assumed to act at the spinal level at attenuating mono- and polysynaptic conduction, primarily by inhibiting the release of excitatory transmitters [4, 8, 19, 29]. Baclofen hardly penetrates the blood-brain barrier; therefore, penetration into the cerebrospinal fluid (CSF) is poor with oral administration. With oral doses of 100 mg the CSF concentration varied between undetectable and 95 ng/ml. As many as 30% of patients with severe spinal spasticity are unresponsive to oral baclofen or experience intolerable side-effects at effective doses.

Penn and Kroin [23] were the first to report good results with continuous intrathecal baclofen infusion (CIBI) in patients with severe spinal spasticity. A dramatic clinical improvement was reported [21, 23, 24]. Further experimental studies followed and it could be shown that CSF concentrations of 130–950 ng/ml were achievable with CIBI in doses ranging between 0.05 and 1.2 mg/day [10, 16]. On the other hand, plasma concentrations were below 5 ng/ml, which is 100 times lower than with maximum oral medication [16, 21]. There are numerous reports of

CIBI in the treatment of spinal spasticity [6, 7, 11, 12, 15, 18, 22, 25, 28, 30] and today CIBI is considered to be the treatment of choice in these patients.

Spasticity of supraspinal origin is much more common than spinal spasticity, but treatment with CIBI has been evaluated far less frequently in this condition. Reports of successful treatment of patients with supraspinal spasticity are limited [2, 3, 6, 9, 15, 26]. Especially patients with severe traumatic and/or hypoxic brain injury often suffer from severe tetraspasticity that is unresponsive to oral medication, physiotherapy or other antispastic therapies.

In this paper we report our results in treating 18 patients with severe spasticity following traumatic or hypoxic brain injury.

Patients and methods

The first patient, a 31-year-old female, who suffered a severe brain injury, was first treated in 1991. She developed severe tetraspasticity about 1 month after the insult. To achieve sufficient mechanical ventilation sedatives were necessary and weaning from the respirator was impossible in this situation. Oral antispastic medication had no effect, but the results of an intrathecal baclofen bolus injection were very good. After repeated intrathecal bolus injection (50 μg) spasticity nearly disappeared. It was possible to discontinue sedatives and mechanical ventilation. A programmable electronic pump device (Medtronic, Synchromed 8611 H) was implanted and the patient was soon sent for rehabilitation. Her Ashworth score decreased from 4.5 to 1.5. At discharge the daily intrathecal baclofen dose was 200 μg. The dose was gradually reduced to 115 μg/day over the next 2 years. There was no further change in the Ashworth score. The patient is in a vegetative state and now lives in a nursing home.

All the other patients were admitted by rehabilitation centres or nursing homes. Prior to admission all of them were treated with maximum doses of various oral antispastic agents. Other treatments, like peripheral nerve blocks, botulinum toxin or selective posterior rhizotomies have not been attempted because of the patients' diffuse spasticity, which affects the whole body (limbs, trunk, head and neck). The interval between event and bolus test varied between 1 and 62 months (median, 7 months).

In all patients the intrathecal baclofen bolus test was indicated because nursing and physiotherapy were impossible or provoked severe spasms. Most patients suffered severe pain from nursing and physiotherapy. Decubital ulcers, immobility and in some cases autonomic dysregulation should be mentioned as additional indications.

In all patients the response to intrathecal baclofen was tested with repeated bolus applications of 50–100 μg baclofen before pump implantation. The response was rated positive when the Ashworth score decreased at least about one point 4 h after bolus application. Each bolus did not exceed 100 μg for two reasons: first, there is a risk of respiratory complications; and second, there are good reasons for assuming that patients responding inadequately to 100 μg baclofen would need very high doses (> 1000 μg/day) of intrathecal baclofen to achieve sufficient reduction of muscle tone. CIBI then becomes a very expensive form of therapy.

So far 19 patients have participated in the bolus test. All had a positive response to the test, which means a reduction in Ashworth scale score of at least one point with doses up to 100 μg. One of the patients did not have a pump implanted for CIBI, although he experienced a reduction in muscle tone. The patient presented in a vegetative state and with severe autonomic dysregulation, as part of the midbrain syndrome. It was recommended that the patient receive intermittent symptomatic therapy with sedatives and antiadrenergic medication. He died a few weeks later from the autonomic dysregulation.

All other patients were considered to be candidates for CIBI and a pump was implanted. Muscle tone and spasms were assessed at admission and at discharge according to the Ashworth and Spasm frequency scores (Table 1). For the assessment, the patient's highest Ashworth score was always noted. In patients 1 and 2 we saw a significant difference in Ashworth score between the right and the left side. In these two patients the mean Ashworth score was calculated for both sides. Additional assessments, for instance of function and pain, were difficult or even impossible in these patients. Pain was assumed when patients made typical, pain-associated gestures and facial movements.

Table 1 Definition of Ashworth and Spasm frequency scores as described by Penn [21]

Ashworth score	Muscle tone
1	No increase in tone
2	Slight increase in tone, giving a "catch" when affected part is moved in flexion or extension
3	More marked increase in tone but affected part easily flexed
4	Considerable increase in tone, passive movement difficult
5	Affected part rigid in flexion or extension
Spasm score	**Frequency of spasms**
0	No spasms
1	Mild spasms induced by stimulation
2	Infrequent full spasms occurring less than once per hour
3	Spasms occurring more than once per hour
4	Spasms occurring more than 10 times per hour

Results

The age of the 18 patients presented was 2.5–70 years, with a mean of 41. Six patients suffered from severe traumatic brain injury. Three had severe multiple trauma with head injury but brain damage predominantly resulted from hypoxia. Nine patients had hypoxic brain injury from strangulation, status asthmaticus, cardiac arrest or subarachnoid haemorrhage with global cerebral ischaemia or infarction. One patient was mildly disabled, 5 severely disabled and 12 were in a vegetative state (Table 2). For the mildly disabled patient transfer to the wheelchair (with the help of 2 persons) was still possible, but difficult. He was partially independent (for eating, drinking). All other patients were totally dependent. Twelve patients were bedridden and 6 partially mobile. Eleven patients presented with decubital ulcers at admission. The ulcers appeared in various locations, most often on the feet and toes and over flexor tendons. Further clinical characteristics are shown in Table 2.

Table 2 Patient characteristics (*SBI* severe traumatic brain injury, *HBI* severe hypoxic brain injury, *GOS* Glasgow outcome scale, 2 = vegetative, 3 = severely disabled, 4 = mild disability)

Patient No.	Age (years)	Sex	Event	Date of event	Date of implantation	Interval to implantation	Outcome after primary event	Impairments before pump implantation
1	31	f	SBI	11/91	12/91	1 month	GOS 2, midbrain syndrome	Weaning from mechanical ventilation impossible
2	44	f	HBI	09/92	05/94	20 months	GOS 3, following simple commands	Perineal care impaired, bedridden
3	30	m	SBI	07/92	07/94	24 months	GOS 3, following simple commands	Upper + lower extremities flexed, contracture of right knee (40°), decubital ulcers over hamstring tendons
4	67	m	HBI	06/94	01/95	7 months	GOS 2	Contracture of right elbow and knee in 90° flexion after fracture and impaired mobilization (spasticity), decubital ulcer on left lateral toe
5	33	f	HBI	01/94	08/94	7 months	GOS 2	Severe flexion spasticity, decubital ulcers, right knee and calf, left elbow, hyperhidrosis, painful frequent spasms
6	25	m	HBI	07/94	02/95	7 months	GOS 2	Decubital ulcers left lateral foot, right and left ax illa, perineal and axillary sores, sitting in wheelchair and standing impaired
7	37	m	HBI	03/94	10/94	7 months	GOS 3, following simple commands	Severe flexion of upper and lower extremities with decubital ulcers at both knees, severe hyperextension of neck, mobilization and perineal care impossible
8	50	f	HBI	12/93	01/95	13 months	GOS 3, following simple commands and communicating	Severe frequent full spasms, decubital ulcers in lateral upper thoracic region from flexed arms and on right lateral toes, pain-induced psychotic episodes, mobilization and nursing only possible with sedatives
9	25	m	SBI	06/94	02/95	8 months	GOS 2	Severe tetraspasticity with massive pain-induced gestures and facial movements
10	38	m	SBI	03/90	05/95	62 months	GOS 2	Decubital ulcer left lateral toes, mobilization impossible because of frequent truncal extensor spasms
11	60	m	SBI	01/94	04/95	15 months	GOS 4	Painful flexion spasticity of left side after right-sided cerebral haemorrhage, extension and standing on right leg impossible
12	37	m	SBI	12/94	04/95	4 months	GOS 2, occasionally following commands	Left arm fixed in flexion, right arm extended and both legs fixed in extension and adduction, mobilization impossible
13	30	m	HBI	05/95	09/95	4 months	GOS 3, following simple commands, single words	Vegetative dysregulation, mobilization and physiotherapy impossible, decubital ulcers occipital and both heels; prior to intrathecal baclofen therapy unable to talk, eat to move
14	47	m	SBI	06/95	10/95	4 months	GOS 2	Decubital ulcers left big toe, heel and right ankle, perineal care and mobilization impossible
15	27	m	SBI	02/89	05/89	3 months	GOS 2	Right-sided spasticity, arm flexed, leg extended, left-sided hemiballism-like movements, multiple decubital ulcers lower limbs and skin lesions
16	70	f	HBI	10/95	04/96	6 months	GOS 2	Decubital ulcer over coccyx, spasticity-provoked severe pain gestures and facial movements
17	44	m	SBI	11/95	05/96	6 months	GOS 2	Nursing and positioning severely impaired, decubital ulcers on both feet, mycosis in perineal and axillary regions
18	46	m	HBI	06/95	05/96	11 months	GOS 2	Contractures of both arms in flexion and legs (knees) in extension

The Ashworth and Spasm frequency scores of all patients are shown in Table 3. All patients responded to intrathecal baclofen infusion with a reduction of muscle tone and spasms. The mean Ashworth score decreased from 4.5 to 2.33, i.e. affected limbs, where passive movements had been nearly impossible, later showed only a slight increase in tone and could be moved easily. The mean Spasm frequency score decreased from 2.16 to 0.94,

Table 3 Spasticity and baclofen dosage in the treatment course

Patient no.	Before implantation		After dose titration		Last follow-up		Months after implantation	Intrathecal baclofen dose at	
	Ashworth score	Spasm score	Ashworth score	Spasm score	Ashworth score	Spasm score		Discharge	Last follow-up
1	4,5	2	1,5	1	2	1	54	200	115
2	4,5	1	2	1	2	1	25	110	105
3	5	3	2	1	2	1	23	100	100
4	3	1	2	0	2	0	17	450	500
5	5	4	2	2	2	2	22	500[a]	500[a]
6	3	1	2	0	2	0	16	200	200
7	5	2	3	1	3	1	20	480	480[b]
8	5	4	3	3	3	2	17	350[c]	350[c]
9	4	0	2	0	2	0	16	200	200
10	5	3	2	1	2	1	13	200	145
11	5	0	2	0	2	0	14	200	200
12	5	3	3	1	3	1	14	500	600
13	5	3	2	1	2	1	11	400	500
14	4	1	2	0	2	0	8	400	400
15	4	3	3	2	4	3	After removal of pump	400	–
16	4	3	2	1	2	1	3	200	250
17	5	3	3	1	2	1	3	350	350
18	5	2	3	1	3	1	3	350	350

[a] Additional intrathecal application of 0.35 mg morphine/day
[b] Additional intrathecal application of 0.6 mg morphine/day
[c] Additional intrathecal application of 2.5 mg morphine/day

Table 4 Clinical outcome after pump implantation

Patient no.	
1	GOS 2, vegetative state, spontaneously breathing 1 week after pump implant, temporary mobilization in wheelchair
2	Temporary mobilization in wheelchair, nursing and perineal care easier
3	Contracture unchanged, decubital ulcers healed, temporary mobilization in wheelchair
4	Contracture unchanged, decubital ulcers healed, temporary mobilization in wheelchair
5	Pain-induced gestures and facial expressions very rare associated with infrequent spasms, decubital ulcers healed, temporary mobilization in wheelchair
6	Remission of perineal and axillary inflammation and decubital ulcers, sitting more than 5 h in wheelchair, standing in standing frame
7	Posture normalized, decubital ulcers healed, temporary mobilization in wheelchair, additional morphine necessary for significant reduction of spasticity
8	Decubital ulcers healed, except right lateral toe (amputation), extension in elbow only to an angle of 100° possible, sufficient nursing without sedatives and temporary mobilization possible
9	Spasticity reduced, no more pain-induced gestures and facial expression, temporary mobilization in wheelchair
10	Complications: seizures after intrathecal baclofen bolus (100 μg) and spinal catheter displacement; decubital ulcer improved, temporary mobilization in wheelchair
11	Extension of left extremities possible, standing on left leg still impossible with an extension deficit of 20°
12	Extension and abduction of left arm possible, right arm no spasticity, hip abduction and flexion possible, contracture of knees in extension unchanged; nursing and mobilization much easier
13	Mobilization and physiotherapy now possible, speaking simple phrases, eating, drinking, tracheostomy occluded, no decubital ulcers
14	Global reduction of spasticity with better possibilities for nursing and mobilization
15	Pump implantation at a different location 05/89, sufficient reduction of spasticity for 6 years, admitted 11/95 with infected subcutaneous pocket, removal of pump, 01/96 new implant indicated with severe spasticity and hemiballismlike movements, after clinical improvement second infection and pump removal, no new implant, spasticity worse
16	No more pain-induced gestures and facial expressions, decubital ulcers healing
17	Decubital ulcers healing, nursing and mobilization easier, no mycosis
18	Still contractures in elbows and knees, pain free, flexion and abduction in shoulders and hip now possible, mobilization in wheelchair possible

which means that overall spontaneous full spasms did not appear any more.

The major therapeutic goals, to improve the feasibilities of sufficient nursing and physiotherapy and to reduce pain were achieved in all patients. In general, spasticity was reduced more in the lower than in the upper limbs. Even torticollis-like twisting of the neck (as indicated in Fig. 1) was positively influenced.

Transfer to wheelchairs was easier and patients were able to sit in them longer. Of the 12 bedridden patients, at least 8 could be temporarily mobilized in wheelchairs; for 3 patients mobilization in bed was possible for the first time and only in 1 patient was the situation unchanged. Of the 6 patients who were already partially mobilized before pump implantation, 3 improved further, in 1 the situation was unchanged and in 2 of the most recent cases assessment has not yet been completed.

In a few patients limb contractures limited effective mobilization to some extent. Six patients presented with limb contractures. In 4, mobilization was not as good as in patients without contractures, but was still possible. Patient 11 with hemispasticity had limited extension in the left knee and was still not able to walk. Patient 12 was mobilized better in bed, but not in the wheelchair. Even in these patients pain could obviously be reduced and nursing, especially perineal care, was easier.

A further therapeutic effect was the prevention, or improved healing, of decubital ulcers. Eleven patients had decubital ulcers at admission. In 5 patients the ulcers healed completely during the course of treatment and in 5 they improved. Patient 8 developed a necrosis of one toe, which was later amputated. The detailed clinical outcome is presented in Table 4.

The motivation of relatives, physiotherapists and nursing staff was much higher once the patients changed from painful agonizing spasticity to a more relaxed condition. Daily baclofen doses varied between 100 and 600 μg with a mean of 265 μg/day. In 3 patients, additional low-dose intrathecal morphine was necessary to reduce pain and spasticity.

The follow-up period currently ranges from 13 to 54 months. There was no tendency towards a further increase in baclofen dose once the dose titration was completed.

Complications derived from the surgical procedure and medical complications were rare. One infection in the pump pocket led to the removal of the system. One patient had an epileptic seizure with the first bolus application of baclofen. It was a single event and there were no further convulsions. In 1 patient the spinal catheter had retracted into the subcutaneous pocket, leading to a rapid loss of efficacy of CIBI. After repositioning of the catheter there were no further complications.

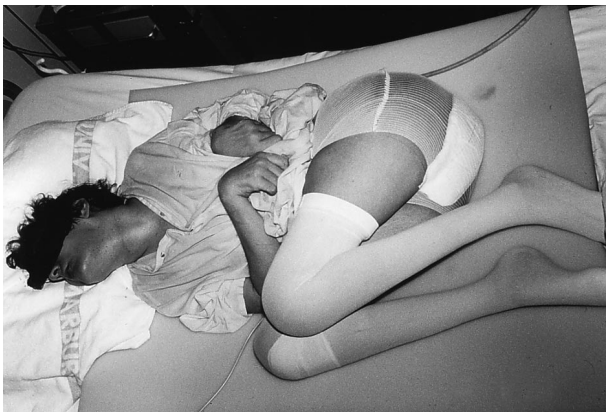

Fig. 1 Thirty-three-year-old female patient (no. 5) with severe hypoxic brain injury, 8 months after strangulation. Ashworth score: 5; Spasm score: 4

Discussion

The clinical course of patients with severe traumatic or hypoxic brain injury is characterized initially by a variable period of deep coma. A midbrain syndrome with flexion and extension spasms and severe dysregulation often persists for months. In the further course many patients die from autonomic dysregulation or severe infections. Patients surviving this stage regularly remain in a vegetative state for a variable period and end either in a persistent vegetative state or are severely disabled. Most of these patients develop severe spasticity from their diffuse supraspinal injury. This spasticity is characterized by continuously increasing muscle tone and increasing frequency of spasms. The response to oral antispastic medication is often limited and physiotherapy becomes more and more difficult. Bizarre defective postures and limb contractures develop (as shown in Fig. 1). Spasticity in these patients is painful, nursing becomes more and more difficult and some patients even develop decubital ulcers.

Severe spasticity of spinal origin and from multiple sclerosis has been proved to be a good indication for CIBI. Long-term data on nearly 600 spinal spasticity patients are available. Spasticity of supraspinal origin is far more common than spinal spasticity, but reports about CIBI in this condition are very rare. Only 143 patients have been treated in three controlled studies. Evaluable long-term data exist for 110 patients. Ciba Geigy kindly provided us with these data, which have not yet been published in full. Seventy-nine patients were paediatric and 31 were adults. Ninety-seven were cerebral palsy patients and only 13 patients had head injuries. Mean drug exposure was 19.1 months. Spasticity was reduced significantly and patients had an improvement in activities of daily living. More detailed data on these improvements are not yet available. The average daily dose at 2 years

was 333 μg (range 60–1200 μg/day); of these patients, 90% required less than 500 μg/day.

The results of the 18 patients enrolled in this study were good. The major therapeutic goals, to make nursing, mobilization and physiotherapy easier and to reduce pain, were achieved. However, it was our impression that the benefit from mobilization and physiotherapy was limited in some patients by already fixed limb contractures that developed with longstanding severe spasticity. Even in these patients we saw a marked reduction in pain. An intraindividual dose-dependent reduction in muscle tone has been reported [3] and was observed in our study too. A further observation in our study was that there seems to be no interindividual correlation between the severity of spasticity and the dose required for sufficient reduction in muscle tone. In 3 cases the additional application of low-dose intrathecal morphine was beneficial. Assessment of pain in these patients could only be achieved by careful observation and the decision to give additional morphine was made almost instinctively.

In the literature we could find only one patient series similar to ours. Rifici et al. [26] reported eight patients with severe traumatic brain injury and good results using intrathecal baclofen. The mean Ashworth score in Rifici et al.'s study was reduced from 3.9 to 1.6. These data correspond to ours. Albright et al. [2, 3] reported in their series of children and young adults with spasticity of cerebral origin a significant reduction of muscle tone in the upper and lower limbs. With CIBI the mean Ashworth score in the lower limbs was reduced from 4 to 2. In the upper extremities the reduction in tone was milder but still significant. Albright et al. further noticed that nursing, perineal care and mobilization became much easier and that pain and the frequency of decubital ulcers decreased. The reduction of muscle tone in studies of supraspinal spasticity patients is comparable to that reported in series of spinal spasticity patients. Ochs et al. [18] and Penn et al. [25] reported a reduction in tone from 3.6 to 1.8 and from 4.0 to 1.2, respectively, in two large series of patients with spinal spasticity.

There are still not enough data from controlled studies on CIBI in supraspinal spasticity patients. Recommending this treatment for all types of supraspinal spasticity, i.e. infantile spastic paresis, hemiparesis and spastic tetraparesis from severe traumatic or hypoxic brain injury, must be done with caution. As Sindou and Mertens [27] have already stated, intrathecal baclofen is not a panacea. Comprehensive therapy of harmful spasticity should take into consideration physiotherapy, intrathecal application of antispastic agents and neuro-ablative techniques. Peripheral neurotomies, motor point and nerve blocks, percutaneous thermo-rhizotomies, intrathecal chemical rhizotomies or open microsurgery selective dorsal rhizotomies and DREZ (Dorsal Root Entry Zone) lesions are highly effective techniques. However, these forms of therapy are indicated in cases of severe spasticity localized to the limbs of para-, tetra- or hemiplegic patients [1, 27]. In diffuse spasticity, as was present in these 18 patients, these ablative techniques have their limitations. Maybe they should be considered as additional options after the primary use of intrathecal baclofen.

Looking at the first case, which was first treated in 1991, one has to consider the *early* use of intrathecal baclofen, even in the intensive care unit. The patient presented here responded very well to intrathecal baclofen. Sedatives and mechanical ventilation could soon be discontinued and the patient was sent for rehabilitation. In this case the time in the acute medical setting was clearly reduced, which might compensate to some extent for the undoubted high costs of CIBI. It is hard to decide whether this treatment is more expensive than others. A cost benefit analysis seems hardly feasible. Multiple factors have to be taken into account, including the expense of physiotherapy, medical supplies, time needed for nursing, frequency and length of stay in an acute medical setting and finally the cost of antispastic medication.

Considering only drug expenses, one has to reckon DM 6.74 for a daily dose of 500 μg intrathecal baclofen, which is a high dose for a patient with severe spasticity. Compared with this an oral dose of 100 mg baclofen day costs about DM 3.90. However, most of the patients with severe spasticity receive two or three antispastic agents. Daily expenses of DM 8–10 are easily reached (24 mg tizanidine ~ DM 4.50). Meticulous documentation of treatment costs in a case-control study would be required for an exact cost benefit analysis. Nance et al. [17] reported the hospitalization costs resulting from spasticity in six patients. Total costs of Canadian $ 305.688 accumulated within 2 years. In the 2 years after initiation of intrathecal baclofen therapy there were no cases of hospitalization directly resulting from spasticity. Costs for pump implantation and hospitalization due to complications were around Canadian $ 160.000. Net savings of Canadian $ 153.120 resulted for the six patients. However, in this calculation costs for nursing, physiotherapy, medication and the influence on survival time in these severely ill patients were not taken into consideration.

Further controlled studies will be needed to obtain more information about the benefit this heterogeneous group of patients with supraspinal spasticity has from CIBI. These studies have to be designed carefully and cost benefit analyses will be of special interest. Patient assessment is inexact because function and pain are difficult to evaluate in these patients.

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