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Original Article

Intrathecal baclofen in tetraplegia of spinal origin: efficacy for upper extremity hypertonia

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Study design: Retrospective analysis.
Objectives: To evaluate the efficacy of intrathecal baclofen (ITB) for upper extremity spastic hypertonia in tetraplegia of spinal origin.
Setting: University of Alabama at Birmingham hospital.
Methods: The medical records of 14 individuals with tetraplegia of spinal origin who underwent intrathecal baclofen pump placement were reviewed. The effects of intrathecal baclofen on spasm frequency, deep tendon reflexes, and tone (Ashworth scale) were assessed for the upper and lower extremities for a 1-year follow-up period.
Results: There were statistically significant declines in upper extremity spasm scores (1.8 points, $P=0.012$), reflex scores (1.4 points, $P<0.0001$) and Ashworth scores (0.6 points, $P<0.0001$) for the 1-year follow-up period. For the lower extremities, all decreases were significant ($P<0.0001$). There was also a statistically significant ($P<0.0001$) increase in intrathecal baclofen dosage requirements during the 1-year follow-up period to maintain the reductions in spasm frequency, reflexes and tone.
Conclusions: Intrathecal baclofen is a safe and effective intervention for treating upper extremity hypertonia of spinal origin. In addition, the level of intrathecal catheter placement is felt to be of importance.
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Keywords: spinal cord; tetraplegia; intrathecal baclofen; hypertonia; spasticity

Introduction

Cervical injuries of the spinal cord frequently lead to hypertonia characterized by disabling spasticity and dystonia involving the upper and lower extremities. In this setting, spasticity is defined as a velocity-exaggerated increase in tonic stretch reflexes (muscle tone) resulting from hyperactivity of the stretch reflex.[1–3] Acquired dystonia is a persistent attitude or posture of the extremities, such as an overextension or overflexion of the hand, inversion of the foot, or torsion of the spine associated with twisting, lateral bending, or torsion of the back.[4]

Severe cases of hypertonia can be refractory to commonly used oral medications including baclofen. In contrast, the intrathecal delivery of baclofen has been shown to be effective for refractory hypertonia due to a number of processes that cause spinal cord pathology.[5–14] Baclofen, 4-amino-3 (p-chlorophenyl) butyric acid, is felt to work by binding to inhibitory presynaptic GABA-B receptors in the spinal cord.[1] Intrathecal delivery of the drug facilitates achievement of therapeutic levels in the cerebrospinal fluid (CSF) while minimizing systemic side effects (ie, drowsiness or confusion).[1,5–8]

Prior studies examining the efficacy of intrathecal baclofen (ITB) for hypertonia of spinal origin have presented results solely on efficacy in the lower extremities.[5,6,9–11] To our knowledge, there are no citations in the medical literature that provide objective evidence for the efficacy of intrathecal baclofen when treating upper extremity hypertonia of spinal origin. To address this issue, a retrospective analysis was performed to specifically examine and define the magnitude of effect on upper extremity hypertonia secondary to spinal pathology.

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The importance of catheter placement is also broached as the lumbar-to-cisternal CSF concentration for baclofen is 4.1 : 1 and, subsequently, the lack of reported results concerning upper extremity hypertonia could be due to the placement of pump catheters at lower thoracic/lumbar levels.[15] In the medical literature, pump catheters have been primarily reported as being placed in the intrathecal space between approximately T10 and L2,[5–7,11–13,16] although a few investigators have hinted at the importance of catheter placement with spinal cord pathology.[16–18] In contrast to spasticity of spinal origin, midthoracic catheter placement for upper extremity hypertonia has been evaluated for traumatic brain injury and cerebral palsy, and subsequently found to be efficacious.[1,18–21] From clinical observation, it was our impression that by threading the catheter cephalid to approximately the T6 level, one could achieve significant reductions in upper extremity hypertonia in persons with spinal cord pathology as well.

Methods

Subjects

The medical records of patients who underwent baclofen pump placement from October 1995 to November 1999, under the auspices of the Departments of Physical Medicine and Rehabilitation and Neurosurgery at the University of Alabama at Birmingham, were reviewed. Patients with spinal cord pathology afflicting the cervical segments (C1–T1) were selected for further analysis. This subset of patients consisted of 14 individuals. These 14 individuals comprised the study cohort. All study subjects had sustained their injuries at least 6 months prior to baclofen pump placement and had failed to respond to treatment with oral agents, including a trial of oral baclofen, or had experienced unacceptable side effects. Other characteristics of study subjects are summarized in Table 1.

Screening procedure

All patients except two were screened via a bolus injection of 50 μg of intrathecal baclofen. A lumbar puncture was performed at either the L3–L4 or the L2–L3 interspace, and 1 cc (50 μg) of baclofen was injected. Data was collected and scored for spasm frequency, deep tendon reflexes, and tone at 1, 2, 4 and 6 h postinjection by the same investigator. Consideration for continuous ITB delivery via programmable pump and intrathecal catheter were given to those who had: (1) a reduction in tone of at least two points on the Ashworth scale in the lower extremities averaged over at least four joint movements (hip abduction, knee extension, knee flexion, and ankle dorsiflexion); or (2) a reduction in the spasm frequency score of at least two points in one lower extremity without untoward side effects. The patients who had a partial response but did not meet criteria for pump placement were given the option of a 75 to 100 μg bolus trial. If they met criteria with the higher dose trial, pump placement was offered.

Pump implantation

The continuous infusion pump and intraspinal catheter system were implanted under general anesthesia with the patient in the lateral decubitus position. the programmable pump was placed in a lower abdominal wall subcutaneous pocket, above the rectus fascia. The catheter was placed into the lumbar subarachnoid space via a percutaneous technique using a 14- or 15-gauge Touhy needle. The catheter, which was premeasured before insertion, was threaded up to the midthoracic (T6) area because all patients had hypertonia that involved the upper extremities. The intraspinal catheter was then tunneled in the subcutaneous space to the programmable pump, completing the procedure. Postoperatively all patients received 24 to 36 h of intravenous vancomycin and gentamicin for infection prophylaxis.

Table 1 Study subject demographics

Subject	*Gender*	*Age*	*Etiology of injury*	*ASIA level*	*Injury duration*
1	Male	51	Tree fell on subject	C6 ASIA C	117 months
2	Male	34	Motor vehicle accident	C7 ASIA C	30 months
3	Male	41	Diving accident	C5 ASIA A	24 years
4	Male	25	Gunshot wound	C4 ASIA C	39 months
5	Male	43	Neurofibromatosis	NA	NA
6	Male	31	Multiple sclerosis	NA	13 years
7	Male	39	Fall	C4 ASIA A	29 months
8	Male	64	Motor vehicle accident	C4 ASIA C	78 months
9	Female	60	Multiple sclerosis	NA	8 years
10	Male	42	Surgery	C4 ASIA D	16 months
11	Female	41	Diving accident	C5 ASIA C	6 months
12	Male	34	Motor vehicle accident	C4 ASIA A	7 years
13	Male	41	Fall	C4 ASIA C	14 months
14	Male	34	Assault	C5 ASIA B	44 months

Outcome measures and follow-up

Prior to pump placement the study subjects had undergone a baseline evaluation, and following pump placement they were re-evaluated at approximately 1, 3, 6, 9 and 12 months. Tone, spasm frequency, and deep tendon reflexes were assessed at baseline and at each subsequent follow-up interval. Tone was measured in the upper extremities (shoulder abduction, elbow flexion, elbow extension, wrist extension) and lower extremities (hip abduction, knee flexion, knee extension, ankle dorsiflexion) using the 5-point Ashworth scale (Table 2). Spasm frequency was recorded in the upper extremities and lower extremities using a 5-point scale (Table 2). Deep tendon reflexes at the biceps, patella, and Achilles were documented with a 6-point scale (Table 2).

At each evaluation, the current 24-h (daily) infused dosage of baclofen was recorded. If indicated, dosage adjustments were made in 10% to 20% increments. Also noted were untoward complications, including cognitive dysfunction, urologic problems, infections, and problems regarding physical and occupational therapy, as well as equipment malfunction.

Statistical analysis

Changes in muscle tone, spasms, and deep tendon reflexes were analyzed using Friedman's test. This was utilized because the muscle tone, spasm, and reflex scores used nonparametric, ordinal level scales, and the Friedman's test is felt to be the nonparametric equivalent of a repeated measures analysis of variance (ANOVA) with a single group.[22] The Wilcoxon signed rank test was also employed to test the significance of observed differences between specific time points during the follow-up period. A value of $P<0.05$ was considered significant. Although nonparametric tests were used, data are presented as averages and standard deviations (SD) to facilitate the interpretation of the magnitude and clinical significance of the results. In addition, for clarity of presentation, rather than reporting tone, spasm, and reflex scores for individual muscles (ie, deltoids, biceps, triceps, etc.), muscles tested for the upper extremities were averaged. Similarly, scores for the lower extremities were averaged as well. Statistical analysis was then performed separately for the upper and lower extremities.

The reliability and reproducibility of the Ashworth scale, spasm frequency scale, and reflex scale have previously been described.[19,23,24] Statistical analysis was performed utilizing StatView 5.0 (Abacus Concept Inc., Berkeley, CA, USA).

Table 2 Definitions of rating scales

Ashworth scale	
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 frequency scale	
0	No spasms
1	Mild spasms induced by stimulation
2	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
Reflex scale	
0	Reflexes absent
1	Hyporeflexia
2	Normal
3	Mild hyperreflexia
4	3 or 4 beats of clonus
5	Clonus

Results

Lower extremities

Following baclofen pump placement, the average Ashworth score (tone) for the lower extremities decreased from 3.1 ± 1.3 (SD) at baseline to 1.7 ± 0.9 (SD) at 12 months ($P<0.0001$, Friedman) (Figure 1). Similarly, the average spasm score decreased from 3.3 ± 0.9 (SD) at baseline to 1.8 ± 1.5 (SD) at 12 months ($P=0.0011$, Friedman) (Figure 2). Reflexes also decreased significantly. The average baseline reflex score was 2.8 ± 1.3 (SD) compared to 0.4 ± 0.9 (SD) at 12 months ($P<0.0001$, Friedman) (Figure 3).

Upper extremities

Similar to the lower extremities, there was a significant decline in upper extremity hypertonia during the 12 month follow-up period. The average baseline Ashworth score was 2.4 ± 1.1 (SD) com-

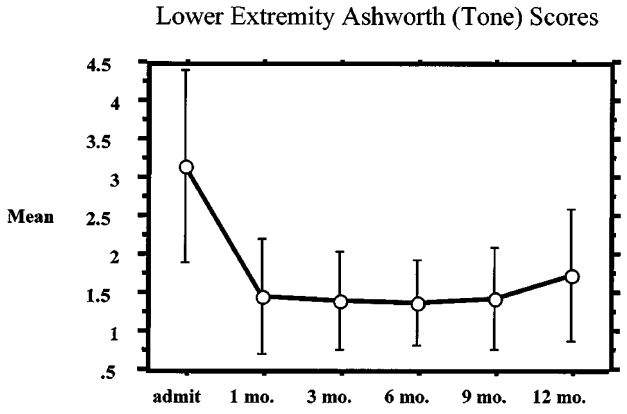

Figure 1 Lower extremity Ashworth (tone) scores with one standard deviation bar

pared to 1.8±1.0 (SD) at 12 months ($P<0.0001$, Friedman) (Figure 4). The average spasm score decreased from 2.3±1.6 (SD) to 0.5±0.9 (SD) but this failed to reach statistical significance ($P=0.2503$) using Friedman's test (Figure 5). The difference was significant ($P=0.0012$) using the less rigorous Wilcoxon signed rank test. The Wilcoxon signed rank test compared the baseline value and final value (12 months) unlike the Friedman's test which assessed the curve throughout the follow-up period. For upper extremity reflexes, the average baseline reflex score was 2.3±0.2 (SD) compared to 0.9±0.2 (SD) at 12 months ($P<0.0001$, Friedman) (Figure 6).

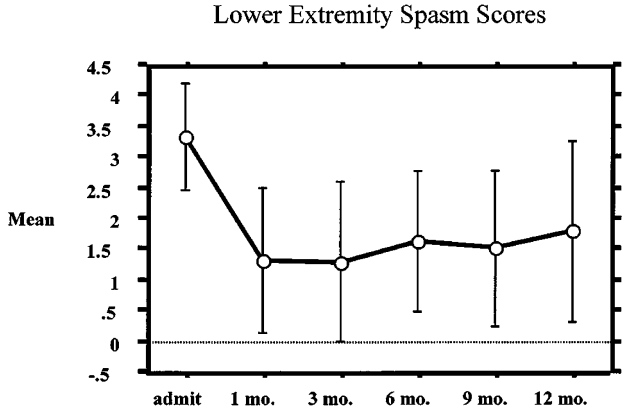

Figure 2 Lower extremity spasm scores with one standard deviation bar

Dosage

Dosage requirements progressively increased during the 12-month follow-up period. This was statistically significant. Average initial dosage requirements were 120.0 μg/day±22.1 (SD) compared to 299.0 μg/day±183.0 (SD) at 12 months ($P<0.0001$, Friedman) (Figure 7).

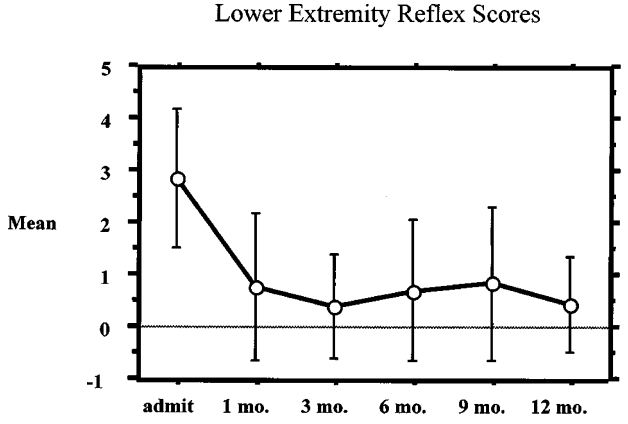

Figure 3 Lower extremity reflex scores with one standard deviation bar

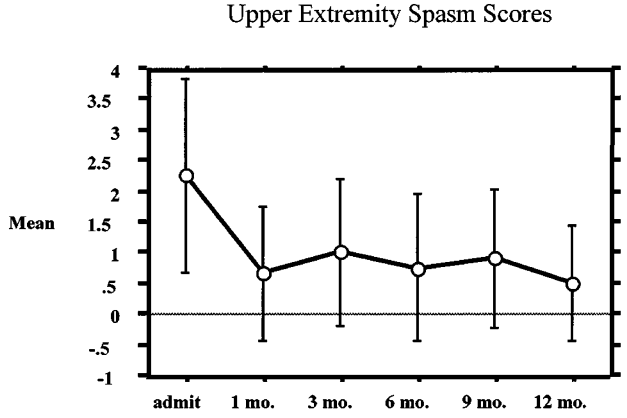

Figure 5 Upper extremity spasm scores with one standard deviation bar

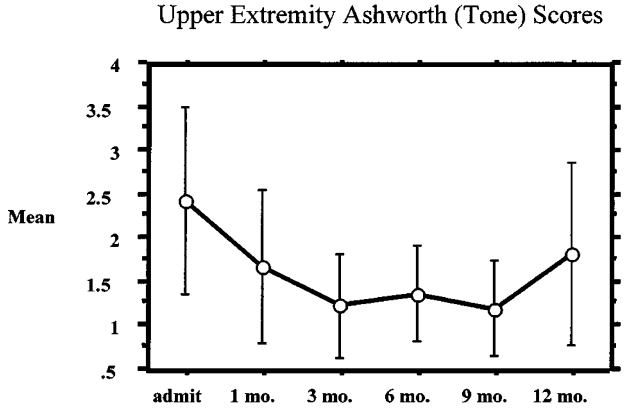

Figure 4 Upper extremity Ashworth (tone) scores with one standard deviation bar

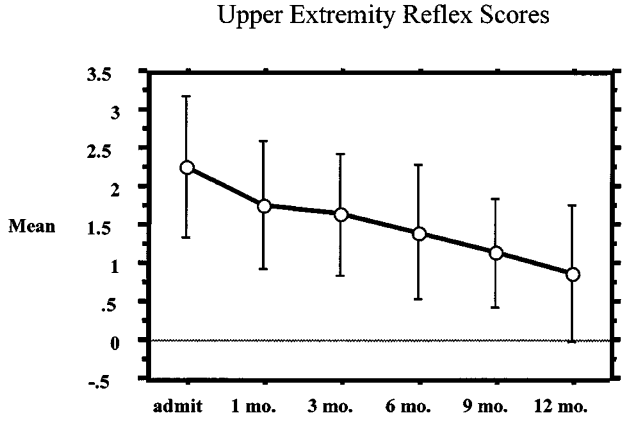

Figure 6 Upper extremity reflex scores with one standard deviation bar

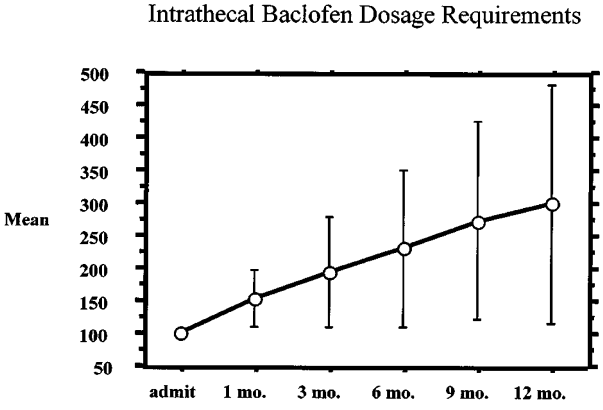

Figure 7 Intrathecal baclofen dosage (μg/day) requirements with one standard deviation bar

Complications

Pump placement was well tolerated by all the patients and there were no significant complications during the 12-month follow-up period. There were no reported cognitive side effects, related seizure breakthroughs, or changes in urinary or fecal voiding patterns. One patient did develop a pocket infection approximately 20 months after pump placement which necessitated surgical replacement, however, this occurred outside the 1-year study follow-up period.

Discussion

Effects on hypertonia

The efficacy of intrathecal baclofen has been clearly demonstrated for refractory hypertonia resulting from a variety of pathologic conditions.[1,5–10,18,21,25–32] Furthermore, intrathecal baclofen has been shown to have an effect on hypertonia in the upper and lower extremities due to supratentorial pathology such as acquired brain injury and cerebral palsy.[1,18–21,28] In contrast, the presence and magnitude of tone reduction has yet to be confirmed and defined for upper extremity hypertonia of spinal origin.

This study is the first to document a statistically significant decrease in Ashworth (tone) and reflex scores in upper extremity hypertonia due to pathology at the level of the spinal cord. Upper extremity Ashworth scores improved from 2.4 ± 1.1 (SD) at baseline to 1.8 ± 1.0 (SD) at 12 months. In comparison, lower extremity Ashworth scores improved from 3.1 ± 1.3 (SD) at baseline to 1.7 ± 0.9 (SD) at 12 months.

The relative difference in magnitude of improvement when comparing the upper extremities to the lower extremities could partially be explained by greater baseline spasticity in the lower extremities. Because of this, there was more room for improvement in the lower extremities compared to the upper extremities. This rationale is reinforced when 12 month Ashworth scores are directly compared in the upper and lower extremities (1.8 ± 1.0 SD *vs* 1.7 ± 0.9 SD). When this is done, one can see that severity of tone in the upper and lower extremities, measured with Ashworth scores, is comparable at 12 months. Similar findings have been noted in the traumatic brain injury and pediatric cerebral palsy populations.[1,18]

There was not, however, a significant decline in spasm frequency with the relatively rigorous Friedman's test. Friedman's test takes into account the shape of the curve during the entire follow-up period, while the Wilcoxon signed rank test examines the magnitude of difference between two defined time-points on the curve. With the less rigorous Wilcoxon, a significant ($P = 0.0012$) difference in spasm frequency was noted between the initial evaluation and the 12-month evaluation.

This is probably the result of several factors. First, the spasm frequency score was dependent on verbal feedback from the patient while the tone and reflexes were objectively measured by the examiner. Secondly, after the initial decline in spasm frequency from initial evaluation to 1 month evaluation (Figure 5), the baseline oscillated. Again, this was probably impacted by patient difficulty in accurately distinguishing between scores on the lower end of the spasm frequency scale. Also, patient numbers might have been insufficient and therefore prevented the decline from reaching statistical significance with Friedman's test. Perhaps most importantly, patients were selected predominantly for disabling lower extremity tone or spasms which may have resulted in a floor effect. The data supports this as the initial tone and spasm frequency scores were much lower in the upper extremities, 2.4 and 2.3 respectively, *vs* 3.1 and 3.3. in the lower extremities.

Like prior studies, our study confirmed the efficacy of intrathecal baclofen for the treatment of refractory lower extremity hypertonia.[1,5–10,18,21,25–32] There were statistically significant decreases in lower extremity tone, spasm frequency, and hyperreflexia following the initiation of therapy with intrathecal baclofen, and the effects persisted for the 12-month follow-up period.

Another interesting finding is that when the upper and lower extremity curves for Ashworth (tone) scores are closely scrutinized, there appears to be a slight increase in tone at 12 months in comparison to the intervening months. This suggests the possible development of early tolerance to intrathecal baclofen. It would be of interest to follow patients for extended periods (>12 months) to see if drug tolerance becomes more of an issue.

It should also be emphasized that patients in this study had their intrathecal catheters threaded to T6 which is significantly higher than what has been traditionally advocated (T10–L2).[5–7,11–13,16] This is important because intrathecal baclofen diffuses rapidly from the intrathecal space into the spinal cord, resulting in a lumbar-to-brain gradient.[1,6,16] Since intrathecal delivered baclofen crosses from the

intrathecal space to the spinal cord quickly, it intuitively makes sense to move the catheter cephalid toward the cervical region for improved upper extremity effects.

Prior attempts to address upper extremity hypertonia by increasing the rate of infusion have resulted in lower extremity hypotonia and functional losses with regards to transfers and activities of daily living.[5] Moving the catheter cephalid could theoretically improve the efficacy of intrathecal baclofen for upper extremity hypertonia by increasing CSF drug concentrations in the upper thoracic and cervical regions. Our study findings appear to support this and are in agreement with what has been previously noted in the traumatic brain injury and cerebral palsy populations.[1,18–21] This deviation from standard procedure was well tolerated by our patients as there were no adverse events in the study population attributable to the change in catheter location.

Therefore, intrathecal baclofen appears to be an effective intervention for upper extremity as well as lower extremity hypertonia of spinal origin. Furthermore, efficacy for upper extremity hypertonia appears to be facilitated by midthoracic (T6) catheter placement. This deviation from traditional catheter placement (T10–L2) was well tolerated and there were no significant complications in our study population.

Dosage requirements

Dosage requirements showed an almost linear increase throughout the 12 month follow-up period. Other investigators have also described a linear relationship.[33] It is our belief that this relationship is secondary to dosage adjustments to optimize efficacy following pump placement along with increasing drug tolerance. Prior studies with intrathecal baclofen have also noted increasing dosage requirements with the passage of time.[1,5,8,33] This has been attributed to the downregulation of GABA-B receptors at the spinal level.[1,33] In our study, the slight increase in tone at 12 months is also suggestive of emerging tolerance. Akman found a significant increase in dosage requirements up until 12 months followed by a leveling off from 12 to 24 months.[33] Others have also suggested a plateauing effect.[10,11,13] When progressive tolerance has become an issue, it has been successfully treated with 'drug holidays'.[8,11–13] In these cases, intrathecal saline or opiates were substituted for baclofen which was later successfully restarted at lower doses.

Therefore, physiologic tolerance does appear to be a real issue during the first year but there is evidence that dosage requirements thereafter stabilize.[33] In order to clarify this issue and its clinical implications, additional long-term (>12 months) studies are needed. This should become a reality as the numbers of patients increase and we continue to gain experience with the use of intrathecal baclofen.

Summary

This study demonstrates that significant reductions in upper extremity hypertonia of spinal origin can be safely achieved using intrathecal baclofen with midthoracic (T6) catheter placement. Improvement can be documented using Ashworth, reflex, and spasm frequency scores for both the upper and lower extremities. Additional studies are needed that examine the effect of improved upper extremity spasticity and dystonia on functional status. Regardless, reductions in hypertonia can ameliorate pain, improve sleep, and facilitate nursing care and hygiene. The natural history of drug tolerance after 1 year and its possible impact on the long-term (>12 months) efficacy of intrathecal baclofen also awaits clarification.

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