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Original Research

Intrathecal Versus Oral Baclofen: A Matched Cohort Study of Spasticity, Pain, Sleep, Fatigue, and Quality of Life

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Abstract

Background: Baclofen commonly is used to manage spasticity caused by central nervous system lesions or dysfunction. Although both intrathecal and oral delivery routes are possible, no study has directly compared clinical outcomes associated with these 2 routes of treatment.

Objective: To compare spasticity levels, pain, sleep, fatigue, and quality of life between individuals receiving treatment with intrathecal versus oral baclofen.

Design: Cross-sectional matched cohort survey study.

Setting: Urban academic rehabilitation outpatient clinics.

Participants: Adult patients with spasticity, treated with intrathecal or oral baclofen for at least 1 year, matched 1:1 for age, gender, and diagnosis.

Methods: Standardized surveys were administered during clinic appointments or by telephone.

Main Outcome Measures: Surveys included the Penn Spasm Frequency Scale, Brief Pain Inventory, Epworth Sleepiness Scale, Fatigue Severity Scale, Life Satisfaction Questionnaire, and Diener Satisfaction with Life Scale.

Results: A total of 62 matched subjects were enrolled. The mean (standard deviation [SD]) age was 46 (11) years with a mean duration of intrathecal baclofen or oral baclofen treatment of 11 (6) and 13 (11) years, respectively. There were 40 (64%) male and 22 (36%) female subjects. Primary diagnoses included spinal cord injury ($n = 38$), cerebral palsy ($n = 10$), stroke ($n = 10$), and multiple sclerosis ($n = 4$). The mean (SD) dose of intrathecal and oral baclofen at the time of survey were 577 (1429) $\mu\text{g}/\text{day}$ and 86 (50) mg/day , respectively. Patients receiving intrathecal compared with oral baclofen experienced significantly fewer (1.44 [0.92] versus 2.37 [1.12]) and less severe (1.44 [0.92] versus 2.16 [0.83]) spasms, respectively as measured by the Penn Spasm Frequency Scale ($P < .01$; $P < .01$). There were no significant differences in pain, sleep, fatigue, and quality of life between groups. Subanalysis of patients with SCI mirrored results of the entire study sample, with significant decreases in spasm frequency and severity associated with intrathecal compared to oral baclofen ($P < .01$; $P < .01$), but no other between group differences. The mean (SD) percent change in dose of oral (21% [33%]) compared with intrathecal (3% [28%]) baclofen was significantly larger two years prior to the date of survey ($P = .02$).

Conclusions: Long-term treatment with intrathecal compared with oral baclofen is associated with reduced spasm frequency and severity as well as greater dose stability. These benefits must be weighed against the risks of internal pump and catheter placement in patients considering intrathecal baclofen therapy.

Introduction

Baclofen, a gamma-aminobutyric acid B (GABA_B) agonist [1], commonly is used to manage spasticity caused by central nervous system lesions or dysfunction [2,3]. Both intrathecal and oral delivery routes are possible. Control of spasticity typically is first

attempted with oral baclofen, as intrathecal delivery requires surgical placement of an internal pump and catheter system, pump battery replacement every 5-7 years, and regular pump reservoir refills at least every 6 months [3-5]. When administered via the oral route, only a fraction of this medication passes the blood-brain barrier, where target GABA_B receptors are

located [6,7], thus necessitating greater doses of medication to achieve the desired effects compared to intrathecal delivery. This potentially results in unwanted side effects, including urinary retention, confusion, drowsiness, sleepiness, dizziness, nausea, and constipation, among other symptoms [6,8-10].

Alternatively, the administration of baclofen via the intrathecal route allows for placement of medication in close proximity to target GABA_B receptors, which allows for the use of much lower doses compared to oral delivery [11-13]. With intrathecal administration, clinicians can use continuous dosing to minimize high peak and low trough medication levels [10]. Additionally, the rate of medication delivery can be customized to change as frequently as every 15 minutes to accommodate variations in spasticity throughout the day [10].

Intrathecal administration of baclofen has been reported to result in greater control of spasticity with fewer side effects compared with oral dosing. However, pump placement requires commitment to periodic pump reservoir fills and surgery, including pump and/or catheter replacements, and is associated with a number of life-threatening complications (albeit rarely). Measurements that reflect the patient's voice in long-term outcomes and quality of life are needed to better inform patient choices in health care options over a lifetime of care [14]. To date, there has never been a direct comparison of treatment with intrathecal versus oral baclofen. The purpose of the present study was to compare patient-centered measures of spasticity control, pain, sleepiness, fatigue, and quality of life in patients treated with intrathecal versus oral baclofen, as each of these outcome domains may be affected differently by the 2 routes of delivery.

Methods

Design

This was a cross-sectional survey of patients receiving either intrathecal or oral baclofen therapy. Surveys were administered prospectively by telephone or at the time of subjects' clinic follow-up appointments. The local institutional review board approved this study, and all subjects gave informed consent for study participation.

Participants

Individuals 18 years of age and older who had been treated with intrathecal or oral baclofen for at least 1 year were recruited from a single-site outpatient academic Physical Medicine and Rehabilitation practice during routine visits between January 2012 and January 2015. Individuals who were not able to understand the consent process because of cognitive impairment were excluded. Clinicians at the study site were asked to

identify patients who had received intrathecal or oral baclofen therapy. Additionally, a list of all individuals on intrathecal baclofen therapy managed at the study location was used to recruit all potential subjects. This list is maintained as a part of routine clinical care to ensure that intrathecal baclofen pump alarm dates are not missed so as to avoid baclofen withdrawal. Electronic medical records also were queried for diagnostic and billing codes to identify patients who met study inclusion criteria, as well as to verify length and dosing of ITB or oral baclofen therapy. Demographic information was extracted from the medical record, which included age, gender, etiology of spasticity (primary diagnosis), duration of time since the initiation of antispasticity medication, whether antispasticity medications other than baclofen were being used, and whether opioid agents were being used. Potential subjects between intrathecal and oral baclofen groups were matched by age \pm 10 years, gender, and etiologic diagnosis of spasticity.

Outcome Measures

Outcome measures were selected on the basis of domains that are known to be affected by baclofen and may be differentially influenced by an intrathecal versus oral route of medication delivery. Subjects completed surveys during their routine clinic appointments or by telephone. Standardized questionnaires chosen to assess the effectiveness of the treatment included:

1. Penn Spasm Frequency and Severity Scale (PSFS). This measure provides a patient rating of spasm frequency, rated in integers from 0 to 4; no spasms (0), mild spasms induced only by stimulation (1), infrequent full spasms occurring less than once per hour (2), spasms occurring more than once per hour (3), and spasms occurring more than 10 times per hour (4), and spasm severity, rated as integers: none (0), mild (1), moderate (2), and severe (3) [15,16].
2. Brief Pain Inventory (BPI). This measure indicates patient reported intensity of pain and pain interference with various activities. Responses are graded on an integer scale from 0 (no pain or pain interference) to 10 (most pain or pain interference imaginable) [17].
3. Epworth Sleepiness Scale (ESS). This measure assesses patient rated level of daytime sleepiness or sleep propensity. The questionnaire solicits the chance that subjects feel that they might doze in 8 specific situations on an integer scale from 0 to 3, with the total score ranging from 0 (no sleepiness) to 24 (high degree of sleepiness) [18,19].
4. Fatigue Severity Scale (FSS). The FSS uses a 7-point Likert scale to rate the level of agreement or disagreement for 9 statements related to fatigue. The scores are averaged, such that a range from

- 1 (no fatigue) to 7 (greatest possible amount of fatigue) is possible [20].
5. Life Satisfaction Questionnaire (LSQ). The LSQ measures global life satisfaction as well as satisfaction in specific domains (leisure, occupation, etc) on a 6-point integer scale. Scores are averaged, such that a range from 1 to 6 is possible, with larger numbers indicating greater satisfaction [21].
6. Satisfaction with Life (SWLS). The SWLS assesses overall life satisfaction with life by using 5 statements rated on a 7-point scale, for a possible total of 0-35 points. Greater numbers indicate greater satisfaction with life [22,23].

In addition, a standardized questionnaire was developed by the authors of this study to assess oral spasticity medication use: the Oral Spasticity Medication Survey. This questionnaire is shown in Appendix A.

Long-Term Baclofen Dose Stability

Long-term baclofen dose stability related to intrathecal versus oral use was evaluated as there is minimal development of a tolerance effect with long-term intrathecal baclofen use [4,24-26], yet there is no available study for comparison of potential long-term tolerance of oral baclofen. The long-term stability of the intrathecal and oral baclofen daily doses was determined by calculating the change in dose between time of survey and 1, 2, and 3 years earlier than time of survey.

Statistical Analysis

A sample size of 31 subjects in each group (intrathecal versus oral baclofen) was required to achieve 80% power to detect a mean of paired differences of 0.5 in the primary outcome PSFS with an estimated standard deviation (SD) of differences of 1 and with an alpha of .05 when a 2-sided paired *t*-test was used. Seventy-seven total individuals were recruited until 31 matched pairs could be matched. Thus, a total of 62 subjects were included for data analysis, whereas 15 were excluded.

All analyses were performed using with SAS version 9.4 (SAS Institute, Cary, NC). Data were checked for implausible values and distributional form by the use of summary statistics and graphical displays. Means and SDs were calculated for normally distributed data and medians and 25%-75% interquartile ranges were calculated for data that was not normally distributed. Two-sample *t*-tests were used to compare continuous data and χ^2 or Fisher exact tests were used to compare categorical data between the intrathecal and oral baclofen groups. Linear regression was performed to control for the potential confounding effect of pain on sleep and quality of life. The level of significance was

set at .05. Two-sided testing was used for all hypothesis testing.

Results

Patient characteristics grouped by intrathecal versus oral baclofen therapy are shown in Table 1. Sixty-two matched subjects were included in this study. The mean (SD) age was 46 (11) years with a mean duration of intrathecal baclofen or oral baclofen treatment of 11 (6) and 13 (11) years, respectively. There were 40 (64%) male and 22 (36%) female subjects. Primary diagnoses included spinal cord injury (SCI) (n = 38), cerebral palsy (n = 10), stroke (n = 10), and multiple sclerosis (n = 4). There were no significant differences between groups with regard to demographics.

Intrathecal and oral baclofen doses annually during the 3 years before the date of survey are shown in Table 2. Long-term intrathecal compared

Table 1
Patient characteristics

Demographics	Intrathecal Baclofen* (n = 31)	Oral Baclofen* (n = 31)	P Value
Age, y			.82
Mean (SD)	45 (11)	46 (12)	
Gender, % (n)			.99
Male	64 (20)	64 (20)	
Female	36 (11)	36 (11)	
Primary diagnosis, % (n)			.27
Spinal cord injury			
Quadriplegia	38 (12)	45 (14)	
Paraplegia	23 (7)	16 (5)	
Cerebral palsy	16 (5)	16 (5)	
Multiple sclerosis	7 (2)	7 (2)	
Stroke	16 (5)	16 (5)	
Duration of time since initiating antispasticity medication			.25
Mean (SD)	11 (6)	13 (11)	
Taking other oral antispasticity medication (tizanidine, diazepam, etc; includes oral baclofen in intrathecal baclofen patients), % (n)			.56
Yes	6 (2)	3 (1)	
No	94 (29)	97 (30)	
Taking opioid medication, % (n)			.20
Yes	13 (4)	26 (8)	
No	87 (27)	74 (23)	
Taking a medication with side effect of fatigue or somnolence, % (n)			.80
Yes	55 (18)	58 (17)	
No	45 (13)	42 (14)	

Medications associated with fatigue of somnolence in this cohort include tricyclic anti-depressants and other agents with anticholinergic properties, antihistaminergic agents, antipsychotic agents, and antiepileptic drugs.

SD = standard deviation.

* Matched by age \pm 10 years, gender, and primary diagnosis.

Table 2
Long-term baclofen dose stability

	Intrathecal (IT)	Oral	P Value
Dose of baclofen at date of survey ($\mu\text{g}/\text{d}$ for IT; mg/d for oral)			
N	29	28	
Mean (SD) ($\mu\text{g}/\text{day}$ for IT; mg/d for oral)	577 (1429)	86 (50)	
Dose of baclofen 1 y before survey			
N	29	23	
Mean (SD) ($\mu\text{g}/\text{d}$ for IT; mg/d for oral)	576 (458)	78 (50)	
Percent change in dose from survey to 1 y previously			
N	28	23	
Mean (SD) ($\mu\text{g}/\text{day}$ for IT; mg/d for oral)	3% (27%)	9% (39%)	.46
Dose of baclofen 2 y before survey			
N	29	21	
Mean (SD) ($\mu\text{g}/\text{d}$ for IT; mg/d for oral)	558 (396)	69 (51)	
Percent change in dose from survey to 2 y previously			
N	29	21	
Mean (SD) ($\mu\text{g}/\text{d}$ for IT; mg/d for oral)	3% (28%)	21% (33%)	.02
Dose of baclofen 3 y before survey			
N	29	24	
Mean (SD) ($\mu\text{g}/\text{d}$ for IT; mg/d for oral)	519 (362)	70 (52)	
Percent change in dose from survey to 3 y previously			
N	28	24	
Mean (SD)	5% (36%)	15% (35%)	.32
Absolute change in dose from T0 to T-1 year			
N	28	24	
Mean (SD) ($\mu\text{g}/\text{d}$ for IT; mg/d for oral)	12 (161)	8 (17)	
Absolute change in dose from T0 to T-2 year (ITB $\mu\text{g}/\text{d}$; oral baclofen mg/d)			
N	28	23	
Mean (SD) ($\mu\text{g}/\text{d}$ for IT; mg/d for oral)	29 (200)	14 (21)	
Absolute change in dose from T0 to T-3 y			
N	28	21	
Mean (SD) ($\mu\text{g}/\text{d}$ for IT; mg/d for oral)	68 (342)	15 (27)	

Absolute and relative dose changes 1 (T1), 2 (T2), and 3 (T3) years before the date of survey (T0) and compared between the IT vs oral group. SD = standard deviation.

with oral baclofen dose stability is shown in [Figure 1](#). Long-term dose stability is more frequent in patients treated with intrathecal compared to oral baclofen. The mean (SD) percent change in dose of oral (21% [33%]) compared with intrathecal (3% [28%]) baclofen was significantly larger 2 years before the date of survey ($P = .02$). There were no significant differences in the mean percent change in dose between groups at 1 or 3 years before the date of survey ($P = .46$; $P = .32$).

Descriptive baclofen treatment questionnaire data and group comparisons are shown in [Table 3](#). Patients receiving intrathecal rather than oral baclofen experienced significantly fewer (1.44 [0.92] versus 2.37 [1.12]) and less severe (1.44 [0.92] versus 2.16 [0.83]) spasms, respectively as measured by the PSFS ($P < .01$; $P < .01$). There were no significant differences in pain (BPI), sleep (ESS), fatigue (FSS), or quality of life (LSQ, SWLS) between groups.

A subanalysis of patients with SCI ([Table 4](#)) mirrored results of the entire study sample, with significant decreases in spasm frequency and severity associated with intrathecal compared with oral baclofen as measured by the PSFS ($P < .01$; $P < .01$), but no other significant differences between groups with regard to pain (BPI),

sleep (ESS), fatigue (FSS), or quality of life (LSQ, SWLS). PSFS scores in patients treated with intrathecal compared with oral baclofen, stratified by the 3 most common diagnoses (SCI, cerebral palsy, and stroke) are shown in [Figure 2](#). For all diagnoses, spasticity is significantly less frequent and less severe in patients treated with intrathecal compared with oral baclofen ($P < .01$ in all cases).

The results of linear regression demonstrated no difference in sleep (ESS) or quality of life (LSQ, SWLS) scores between the patients treated with intrathecal versus oral baclofen when controlling for pain (BPI pain interference score) ($P > .05$ in all cases).

Discussion

The present study is the first to compare clinical outcomes of long-term intrathecal versus oral baclofen use. The results demonstrated significantly lower levels of spasm frequency and severity associated with intrathecal compared with oral baclofen treatment. The mean spasm frequency and severity scores reported by individuals using intrathecal baclofen indicated "spasms induced only by stimulation" that were "mild" in severity. In contrast, the mean spasm

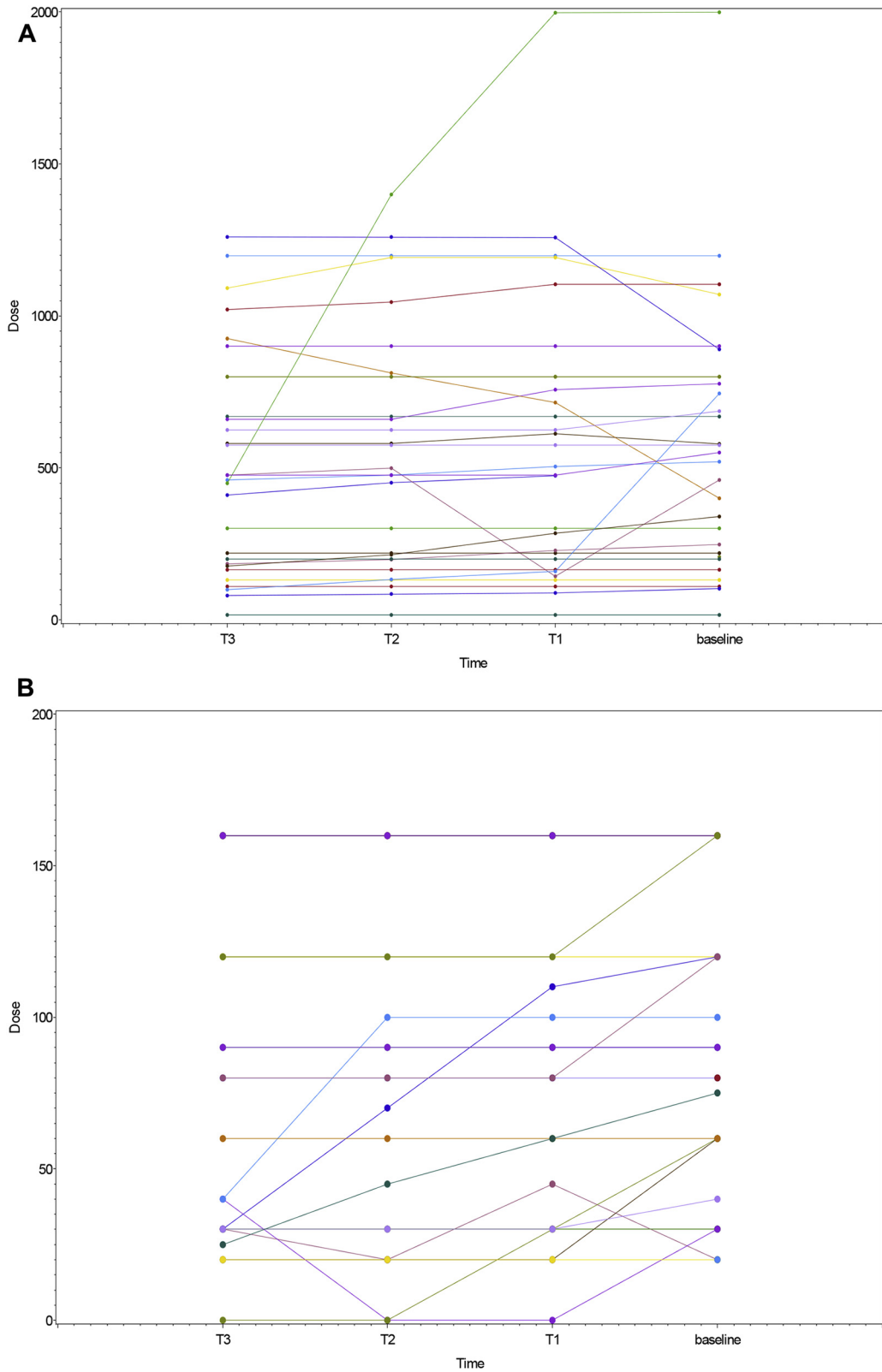


Figure 1. (A) Intrathecal baclofen dose ($\mu\text{g}/\text{day}$) and (B) oral baclofen dose (mg/day) over time, respectively. The baseline dose represents the time of survey and T1, T2, and T3 represent the dose 1, 2, and 3 years before the date of survey, respectively. Each colored line represents a unique patient. Long-term dose stability is more frequent in patients treated with intrathecal compared with oral baclofen.

frequency and severity scores reported by individuals using oral baclofen indicated “infrequent full spasms occurring less than once per hour” that were

“moderate” in severity. These data are consistent with previous reports of spasticity control in patients treated with long-term intrathecal baclofen [4,27].

Table 3
Baclofen treatment questionnaire results for all patients

	Intrathecal		Oral		Intrathecal vs Oral
	Mean	SD	Mean	SD	P Value
Penn Spasm Frequency Scale (PSFS)					
Spasm Frequency Score	1.44	0.92	2.37	1.12	<.01
Spasm Severity Score	1.44	0.92	2.16	0.83	<.01
Brief Pain Inventory (BPI)					
Average NRS pain score	3.79	2.72	5.42	2.81	.22
Worst NRS pain score in last 24 hours	4.21	2.99	6.58	3.31	.13
Least NRS pain score in last 24 hours	2.16	2.43	3.05	2.39	.54
NRS pain score currently	3.05	2.74	4.79	3.24	.20
Pain severity score	3.3	2.54	4.96	2.65	.19
Last 24 hours, pain interfered with:					
General Activity	2.84	3.25	3.16	3.34	.45
Mood	2.89	3.36	2.89	3.97	.80
Relations with other people	1.84	2.75	1.58	2.46	.21
Sleep	4.37	3.71	3.58	3.88	.81
Enjoyment of life	3.11	3.14	3.37	2.75	.38
Pain Interference score	2.84	2.71	2.72	2.42	.99
Epworth Sleepiness Scale (ESS)					
Total score	7.72	6.25	8.16	5.86	.70
Fatigue Severity Scale (FSS)					
Average score	3.26	1.71	3.36	1.52	.68
Life Satisfaction Questionnaire (LSQ)					
Average score	4.14	0.86	4.03	1.25	.39
Diener Satisfaction with Life Scale (SWLS)					
Total score	20.74	6.22	21.63	8.45	.35

SD = standard deviation.

No literature is available for comparison to spasticity control in patients treated with long-term oral baclofen.

Unexpectedly, the present data did not demonstrate a difference between the intrathecal versus oral baclofen group with regard to sleepiness and fatigue,

Table 4
Baclofen treatment questionnaire results for individuals with spinal cord injury

	Intrathecal		Oral		Intrathecal vs Oral
	Mean	SD	Mean	SD	P Value
Penn Spasm Frequency Scale (PSFS)					
Spasm Frequency Score	1.44	0.92	2.37	1.12	.02
Spasm Severity Score	1.56	0.78	2.16	0.83	.03
Brief Pain Inventory (BPI)					
Average NRS pain score	3.79	2.72	5.42	2.81	.13
Worst NRS pain score in last 24 h	4.21	2.99	6.58	3.31	.07
Least NRS pain score in last 24 h	2.16	2.43	3.05	2.39	.30
NRS pain score currently	3.05	2.74	4.79	3.24	.13
Pain severity score	3.3	2.54	4.96	2.65	.11
Last 24 hours, pain interfered with:					
General activity	2.84	3.25	3.16	3.34	.79
Mood	2.89	3.36	2.89	3.97	.99
Relations with other people	1.84	2.75	1.58	2.46	.73
Sleep	4.37	3.71	3.58	3.88	.62
Enjoyment of life	3.11	3.14	3.37	2.75	.81
Pain Interference score	2.84	2.71	2.72	2.42	.90
Epworth Sleepiness Scale (ESS)					
Total score	7.72	6.25	8.16	5.86	.83
Fatigue Severity Scale (FSS)					
Average score	3.26	1.71	3.36	1.52	.80
Life Satisfaction Questionnaire (LSQ)					
Average score	4.14	0.86	4.03	1.25	.76
Diener Satisfaction with Life Scale (SWLS)					
Total score	20.74	6.22	21.63	8.45	.68

SD = standard deviation.

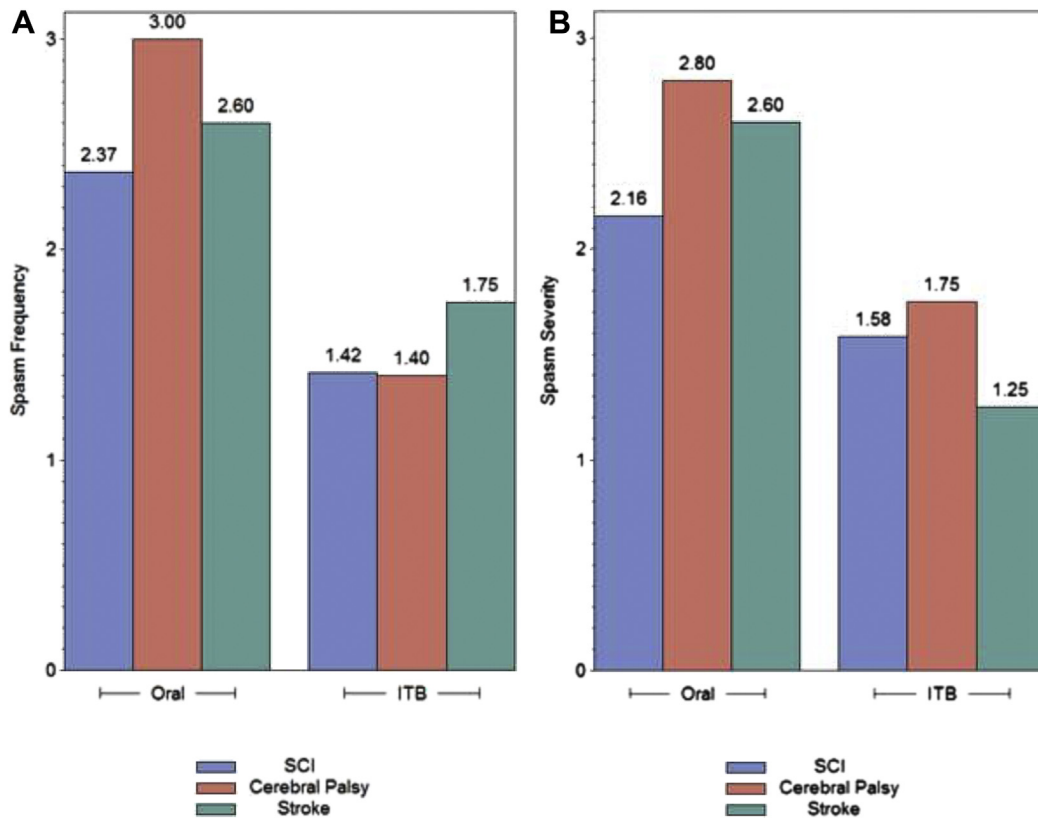


Figure 2. (A) Spasm frequency score (lower is less frequency) and (B) spasm severity score (lower is less severe), respectively, in patients treated with intrathecal versus oral baclofen. Results are stratified into the 3 most common diagnoses: spinal cord injury (blue), cerebral palsy (red), and stroke (green). For all diagnoses, spasticity is significantly less frequent and less severe in patients treated with intrathecal compared to oral baclofen ($P < .01$ in all cases).

2 common side effects of baclofen treatment and purported benefits of intrathecal delivery. This study represents the real-life management of baclofen for patients with spasticity, rather than a randomized study using a dosing protocol, and thus, these findings may be related to the particular cohort studied and the management style of their physicians. In this sample, clinicians generally titrated baclofen to the limit of tolerance with regard to side effects in order to maximize spasticity control as much as possible. At this threshold, superior control of spasticity was possible with intrathecal compared with oral baclofen; however, these data suggest that side-effects may be unavoidable regardless of the route of medication delivery when using this dose management strategy. Further comparative study of intrathecal versus oral baclofen delivery with regard to the severity of other known common side effects of this medication, such as urinary retention, confusion, dizziness, nausea, and constipation [6,8-10] is needed.

This study indicated no difference in global pain in the intrathecal versus oral baclofen groups. It must be noted that, although not statistically significant ($P = .07$), the mean "worst NRS pain score in the last 24 hours" was smaller in magnitude in the intrathecal compared with the oral baclofen group by a margin

of 2.3, exceeding the minimal clinically important difference [28]. It must be noted that "global pain" rating assessed on the BPI pertains to any pain, not just pain associated with spasms. Given that this study was primarily designed to assess differences in spasticity rather than global pain, and that this was a non-randomized sample, the present data do not necessarily indicate that intrathecal compared with oral baclofen more effectively reduces pain, as baseline group differences in pain or other related confounding factors may exist. Rather, these findings suggest that further comparative study of intrathecal versus oral baclofen with regard to decreasing global pain is needed, particularly given the frequency of this problem in individuals with central nervous system lesions or dysfunction [29-32]. Notably, the GABA_b receptor has known antinociceptive properties [33,34] and there is preliminary evidence for pain reduction [35-37], even independent of spasticity control [38-40] associated with intrathecal use in humans.

This study demonstrated no difference in reported quality of life in the intrathecal versus oral baclofen groups. These results must be interpreted cautiously, given the previously mentioned possibility of baseline differences in perceived quality of life between groups. Quality of life is a complex and multifaceted outcome

measure, which would be best evaluated in a randomized comparative study. However, it is notable that individuals with an implanted pump and catheter system requiring regular refills by injection did not report reduced quality of life compared to individuals taking oral baclofen. This finding is consistent with previous study demonstrating that patients managed with intrathecal baclofen viewed "life as a whole" as "rather satisfying" and were "satisfied" or "very satisfied" with their intrathecal baclofen pump in general [4].

This study demonstrated a significant degree of dose stability associated with intrathecal compared with oral baclofen treatment. The mean change in dose of intrathecal baclofen ranged from 3% to 5% in the 3 years preceding survey, whereas the mean change in dose of oral baclofen ranged from 9% to 21% during the same time-period. These finds within the intrathecal cohort are consistent with previous descriptions of minimal dose change with long-term use of intrathecal baclofen [4,24-26]. This is the first description of dose changes of oral baclofen after long-term use and indicates that doses change may be significant, even after a prolonged treatment duration.

Although this study demonstrates advantages in spasticity control and dose stability with intrathecal compared with oral baclofen, these benefits must be weighed against the potential risks of intrathecal baclofen therapy on a patient-to-patient basis. Potential complications associated with intrathecal baclofen therapy include cerebrospinal fluid leak, fistula formation, pseudomeningocele, pump implantation site wound dehiscence, infection, and pump or catheter malfunction [5,11,16,41,42]. Discussion with patients considering intrathecal baclofen therapy regarding these potential risks is necessary.

We aimed to assess patient-centered outcomes in accordance with the Patient Centered Outcomes Research Initiative, which focuses on clinical outcomes of treatments as defined by the patient's experience rather than more objective measurement that may have only an indirect effect on the patient's perception of their own improvement [14]; however, future studies that compare objective outcomes of baclofen treatment via the intrathecal versus oral route are needed. Assessment of reductions in pressure ulcers, contractures, kyphoscoliosis, and cost-effectiveness analysis also would be of value.

Study Limitations

This study is limited by its cross-section design and resulting potential selection bias. Although a randomized, prospective comparison of long-term treatment outcomes of intrathecal versus oral baclofen would be ideal, the logistical challenges of such a trial are considerable. Short of a randomized prospective study, the present cross-sectional design does

provide a high quality of evidence compared with retrospective investigation. Additionally, subject matching by age, gender, and diagnosis minimized study bias. The sample size of this study also limits interpretation of results. Although the study was powered to detect a significant difference in spasm frequency and severity as measured by the PFPS, the primary outcome measure, it was not powered to detect a statistically significant change in overall pain, sleep, fatigue, or quality of life on the measures used.

Conclusions

Long-term treatment with intrathecal compared with oral baclofen is associated with reduced spasm frequency and severity as well as greater dose stability. These benefits must be weighed against the risks of internal pump and catheter placement in patients considering intrathecal baclofen therapy.

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References

1. Dietz V, Sinkjaer T. Spasticity. In: McDonald JW III, Verhaagen J, eds. *Handbook of Clinical Neurology*, Vol. 109 (3rd series). Zurich: Elsevier B.V., 2012, 197-211.
2. Katz RT. Management of spasticity. *Am J Phys Med* 1988;67:108-116.
3. Wahlquist GI. Evaluation and primary management of spasticity. *Nurse Pract* 1987;12:27-32.
4. Mathur SN, Chu SK, McCormick Z, Chang Chien GC, Marciniak CM. Long-term intrathecal baclofen: Outcomes after more than 10 years of treatment. *PM R* 2014;6:506-513.
5. Kofler M, Quirback E, Schauer R, Singer M, Saltuari L. Limitations of intrathecal baclofen for spastic hemiparesis following stroke. *Neurorehabil Neural Repair* 2009;23:26-31.
6. Faigle JW, Keberle H. The chemistry and kinetics of Lioresal. *Postgrad Med J* 1972;48(Suppl 5):9-13.
7. Froestl W. Chemistry and Pharmacology of GABAB Receptor Ligands. *GABAB Receptor Pharmacology - A Tribute to Norman Bowery*. *Adv Pharmacol* 2010;58:19-62.
8. Agarwal SK, Kriel RL, Cloyd JC, et al. A pilot study assessing pharmacokinetics and tolerability of oral and intravenous baclofen in healthy adult volunteers. *J Child Neurol* 2015;30:37-41.
9. Chang E, Ghosh N, Yanni D, Lee S, Alexandru D, Mozaffar T. A review of spasticity treatments: Pharmacological and interventional approaches. *Crit Rev Phys Rehabil Med* 2013;25:11-22.
10. Simon O, Yelnik AP. Managing spasticity with drugs. *Eur J Phys Rehabil Med* 2010;46:401-410.
11. Plassat R, Perrouin Verbe B, Menei P, Menegalli D, Mathé JF, Richard I. Treatment of spasticity with intrathecal baclofen administration: Long-term follow-up, review of 40 patients. *Spinal Cord* 2004;42:686-693.
12. Detrembleur C, Plaghki L. Quantitative assessment of intrathecally administered baclofen in spasticity. *Arch Phys Med Rehabil* 2000; 81:279-284.
13. Albright AL, Thompson Carlos S, Minnigh MB. Cerebrospinal fluid baclofen concentrations in patients undergoing continuous intrathecal baclofen therapy. *Dev Med Child Neurol* 2007;49:423-425.

14. Patient-Centered Outcomes Research. Why PCORI was created. Available at <http://www.pcori.org/content/why-pcori-was-created>. Accessed March 4, 2015.
15. Saval A, Chiodo AE. Intrathecal baclofen for spasticity management: A comparative analysis of spasticity of spinal vs cortical origin. *J Spinal Cord Med* 2010;33:16-21.
16. Albright AL, Gilmartin R, Swift D, Krach LE, Ivanhoe CB, McLaughlin JF. Long-term intrathecal baclofen therapy for severe spasticity of cerebral origin. *J Neurosurg* 2003;98:291-295.
17. Cleeland CS, Ryan KM. Pain assessment: Global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994;23:129-138.
18. Johns MW. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep* 1991;14:540-545.
19. Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep* 1992;15:376-381.
20. Hewlett S, Dures E, Almeida C. Measures of fatigue: Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAFMQ), Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (BRAFNRS) for severity, effect, and coping, Chalder Fatigue Questionnaire (CFQ), Checklist Individual Strength (CIS20R and CIS8R), Fatigue Severity Scale (FSS), Functional Assessment Chronic Illness Therapy (Fatigue) (FACIT-F), Multi-Dimensional Assessment of Fatigue (MAF), Multi-Dimensional Fatigue Inventory (MFI), Pediatric Quality Of Life (PedsQL) Multi-Dimensional Fatigue Scale, Profile of Fatigue (ProF), Short Form 36 Vitality Subscale (SF-36 VT), and Visual Analog Scales (VAS). *Arthritis Care Res (Hoboken)* 2011;63(Suppl 11):S263-S286.
21. Lannem AM, Sorensen M, Frosli KF, Hjeltnes N. Incomplete spinal cord injury, exercise and life satisfaction. *Spinal Cord* 2009;47:295-300.
22. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction With Life Scale. *J Pers Assess* 1985;49:71-75.
23. Pavot WDE. Review of the Satisfaction with Life Scale. *Psychol Assess* 1993;5:164-172.
24. Heetla HW, Staal MJ, Kliphuis C, van Laar T. The incidence and management of tolerance in intrathecal baclofen therapy. *Spinal Cord* 2009;47:751-756.
25. Dario A, Scamoni C, Picano M, Casagrande F, Tomei G. Pharmacological complications of the chronic baclofen infusion in the severe spinal spasticity. Personal experience and review of the literature. *J Neurosurg Sci* 2004;48:177-181.
26. Veerakumar A, Cheng JJ, Sunshine A, Ye X, Zorowitz RD, Anderson WS. Baclofen dosage after traumatic spinal cord injury: A multi-decade retrospective analysis. *Clin Neurol Neurosurg* 2015;129:50-56.
27. Penn RD, Savoy SM, Corcos D, et al. Intrathecal baclofen for severe spinal spasticity. *N Engl J Med* 1989;320:1517-1521.
28. Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *Eur J Pain* 2004;8:283-291.
29. Sezer N, Akkuş S, Uğurlu FG. Chronic complications of spinal cord injury. *World J Orthop* 2015;6:24-33.
30. Creutzfeldt CJ, Holloway RG, Walker M. Symptomatic and palliative care for stroke survivors. *J Gen Intern Med* 2012;27:853-860.
31. Broła W, Mitosek-Szewczyk K, Opara J. Symptomatology and pathogenesis of different types of pain in multiple sclerosis. *Neurol Neurochir Pol* 2014;48:272-279.
32. Tosi LL, Maher N, Moore DW, Goldstein M, Aisen ML. Adults with cerebral palsy: A workshop to define the challenges of treating and preventing secondary musculoskeletal and neuromuscular complications in this rapidly growing population. *Dev Med Child Neurol* 2009;51(Suppl 4):2-11.
33. Enna SJ, McCarson KE. The role of GABA in the mediation and perception of pain. *Adv Pharmacol* 2006;54:1-27.
34. Sawynok J. GABAergic mechanisms in antinociception. *Prog Neuropharmacol Biol Psychiatry* 1984;8:581-586.
35. Slonimski M, Abram SE, Zuniga RE. Intrathecal baclofen in pain management. *Reg Anesth Pain Med* 2004;29:269-276.
36. Loubser PG, Akman NM. Effects of intrathecal baclofen on chronic spinal cord injury pain. *J Pain Symptom Manage* 1996;12:241-247.
37. Herman RM, D'Luzansky SC, Ippolito R. Intrathecal baclofen suppresses central pain in patients with spinal lesions. A pilot study. *Clin J Pain* 1992;8:338-345.
38. Zuniga RE, Schlicht CR, Abram SE. Intrathecal baclofen is analgesic in patients with chronic pain. *Anesthesiology* 2000;92:876-880.
39. Zuniga RE, Perera S, Abram SE. Intrathecal baclofen: A useful agent in the treatment of well-established complex regional pain syndrome. *Reg Anesth Pain Med* 2002;27:90-93.
40. Sanders JC, Gerstein N, Torgeson E, Abram S. Intrathecal baclofen for postoperative analgesia after total knee arthroplasty. *J Clin Anesth* 2009;21:486-492.
41. Zahavi A, Geertzen JH, Middel B, Staal M, Rietman JS. Long term effect (more than 5 years) of intrathecal baclofen on impairment, disability, and quality of life in patients with severe spasticity of spinal origin. *J Neurol Neurosurg Psychiatry* 2004;75:1553-1557.
42. Follet KA, Naumann CP. A prospective study of catheter-related complications of intrathecal drug delivery systems. *J Pain Symptom Manage* 2000;19:209-215.

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Appendix A**Oral Spasticity Medication Survey**

1. What oral anti-spasticity medications do you currently take? What dose?

a. Baclofen (Lioresal)

i No Yes: Dose _____

b. Tizanidine (Zanaflex)

i No Yes: Dose _____

c. Dantrolene (Dantrium)

i No Yes: Dose _____

d. Diazepam (Valium)

i No Yes: Dose _____

e. Other

i No Yes: Dose _____

2. When did you start using oral anti-spasticity medications?

a. Date: _____