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Title: Quantifying the change of spasticity after intrathecal baclofen administration: A descriptive retrospective analysis

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ABSTRACT

Objectives: Exploratory research quantifying the change of spasticity among patients who underwent baclofen intrathecal drug delivery system (IDDS) implantation.

Patients and Methods: 88 patients with a baclofen IDDS were identified. Patient characteristics, spasticity scores pre/post intrathecal baclofen test dose, and IDDS perioperative implantation records were collected. The primary outcome was to quantify the extent to which there was a change in Modified Ashworth Scores (MAS) pre/post-intrathecal baclofen test dose administration. Secondary outcomes included the prevalence of perioperative IDDS implantation complications.

Results: The mean age at IDDS implant was 44.2 years (range, 19–71), and 62.5% were male. 45.5% had spasticity of spinal cord origin, 9% of cerebral origin, and 45.5% of other upper motor neuron dysfunction. Reduction of MAS in the spinal cord origin group was 2.6 (mean, 3.5 to 0.9), cerebral origin group was 2.9 (mean, 3.3 to 0.4), and other origin group was 2.5 (mean, 3.6 to 1.1). In all patients, post dural puncture headache was the most commonly reported complication at 22.7%.

Conclusion: This report offers novel findings documenting a quantifiable change of at least two points on the MAS before and after intrathecal baclofen test dose as statistically significant and could prove to be useful information to enhance the decision making process to proceed with intrathecal baclofen beyond assessment of functional abilities.

1. Introduction

Spasticity is a neuromyotonic hyperexcitable disorder classically characterized by a velocity dependent increase in muscle tone resulting from a complex milieu of afferent, efferent, and local signaling pathways in the spinal cord and central nervous system [1]. The resulting upper motor neuron dysfunction, whether from central brain injury, spinal cord injury, or other neurologic process (i.e. multiple sclerosis) has been well documented to be a significant factor in management of activities of daily living, ambulation, pain, bowel/bladder dysfunction, and overall quality of life [1–3]. Early publications in animal models exploring the application of intrathecal baclofen were intriguing [3,4]. Intrathecal delivery of baclofen provides a concentrated dose of medication to the sites of action (GABA-B receptors) in the central nervous system with much greater efficacy than oral administration, ultimately reducing the experience of adverse effects of the medication with focused delivery when compared to the oral method that requires greater dosing of medication to be used to achieve a central effect [5,6].

Intrathecal drug delivery (IDD) of baclofen was eventually utilized in humans with excellent results [7,8]. The early studies observing outcomes of spasticity relied heavily on functional outcomes. Much of the current knowledge and patient selection criteria was limited to small groups of subjects and retrospective data [9]. Recent studies have looked at larger groups of patients with spasticity, however, most of these studies examined spasticity reduction as a secondary outcome [10,11]. Despite multiple studies confirming the positive impact of

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intrathecal baclofen therapy on patient spasticity outcomes, data pertaining to the clinical utility of using an intrathecal test dose for proper patient selection has not been well described in the literature.

Current clinical practice is based on physician, patient, and caregiver assessment of functional abilities, such as ambulation and completion of activities of daily living. An emphasis is placed on the management of day-to-day activities in an attempt to mitigate potential spasticity related harm (i.e. skin breakdown, pressure sores, infections, patient dependence). In an effort to assist the clinician in diagnosis and appropriate definitive therapy selection, use of a physical assessment tool such as the Modified Ashworth Scale (MAS) can be utilized to support the clinical decision to proceed with intrathecal pump placement. The MAS is a five point spasticity assessment evaluation tool (e.g. range of muscle tone between 0 for normal tone and 5 for complete rigidity/immobility) known to have variations in test-retest and inter-tester reliability, but multiple studies suggest that it is one of the more practical and applicable spasticity assessment tools available to clinicians [12,13].

The objective of this study was to estimate associations between potentially significant factors (e.g. baclofen test dose, diagnostic classification of spasticity, etc.) and clinically important outcomes (e.g. MAS change of spasticity, post-dural puncture headaches, infection, etc) among patients who underwent intrathecal drug delivery system (IDDS) implantation for spasticity management. The primary outcome measure was to quantify the extent to which there was a change in MAS pre- and post-intrathecal baclofen test dose administration. Secondary outcome measures include reporting the prevalence of IDDS-related complications in the perioperative to 24 month follow-up period, particularly clinically documented post-dural puncture headaches and infections.

2. Patients and methods

An institutional review board proposal was approved by Mayo Clinic, Rochester, MN. This cross-sectional study utilized the Mayo Clinic paper and electronic medical records to collect data retrospectively from a cohort of 88 patients who had an IDDS implanted for spasticity management at Mayo Clinic, Rochester, MN. Inclusion criteria was specific to those patients who had failed oral anti-spasmodic agents (e.g. baclofen, benzodiazepines, and centrally acting alpha-2-adrenergic agonists) due to inefficacy, intolerable side-effects, or poor symptom control and had an IDDS implanted (i.e. catheter and pump) using solely baclofen for spasticity management at Mayo Clinic, Rochester, MN during the time period of June 1, 1989 to May 31, 2009. Exclusion criteria included 1) patients with previously implanted IDDS with baclofen referred to Mayo Clinic for baclofen pump management, 2) those who underwent intrathecal test dose therapy only, 3) those implanted prior to the date of recruitment who required revisions of either the catheter or pump, and 4) subjects under the age of 18. A single reviewer (TPP) analyzed all 88 records with independent senior author (MJP) review of five records to ensure inter-rater reliability. Information abstracted from the medical record included 1) patient characteristics (i.e. age, sex, diagnosis), 2) physical examination of each patient's neuromuscular system including sensation, muscle stretch reflexes, gait abilities, strength with manual muscle testing, functional movement such as transfers, ambulation, and activities of daily living, 3) MAS spasticity scores pre- and post- intrathecal baclofen test dose, 4) prior use of oral anti-spasmodic agents such as baclofen, benzodiazepines, alpha-2-adrenergic agonists, and 4) IDDS implantation surgical records in the perioperative to 24 month follow-up period.

3. Statistics

Descriptive analyses were summarized using mean (range) for continuous variables and frequency (percent) for categorical variables and were compared with nonparametric statistics as the data was not expected to follow a traditional distribution. The magnitude of pre- to post-test change in MAS and post-procedural complications were examined with non-parametric Wilcoxon signed rank test and Pearson Chi-square. The extent of spasticity change and age was evaluated using Spearman's rho correlation coefficient. To ensure accuracy and consistency with record review, there was an 80% inter-rater reliability between TPP and MJP ($\kappa = 0.6$). Given the fixed sample size of 88, for continuous outcomes with inter-group differences of ≥ 0.6 the standard deviation, this provided > 0.80 power if the type I error probability associated with these tests was $\alpha = 0.05$. Analyses were conducted using SPSS 21.0 software (IBM Corp, Armonk, NY) at an $\alpha = 0.05$.

4. Results

88 patients who had an IDD with baclofen as monotherapy were identified. The mean age of all patients at IDD implant was 44.2 years (range, 19 to 71), and 62.5% were male. 45.5% had spasticity of spinal cord origin (i.e. spinal cord injury due to traumatic and non-traumatic injury from tumor/mass invasion and/or surgery), 9% of cerebral origin (i.e. cerebral injury due to traumatic brain injury, cerebrovascular events such as stroke, or cerebral palsy), and 45.5% of other upper motor neuron dysfunction (i.e. multiple sclerosis, spastic paraparesis, or Stiff Person Syndrome) (Table 1). All patients demonstrated physical exam findings consistent with upper motor neuron findings, including hyperexcitable muscle stretch reflexes, ambulatory patients exhibited gait disturbances consistent with spasticity, and increased muscle tone with MAS testing. Mean reduction of MAS encompassing all groups pre- to post-test dose was 3.5 to 1.0, respectively. Pre-test MAS had a median value of 4 and an interquartile range of 3 to 4. Post-test MAS had a median value of 1 and an interquartile range of 0 to 1. Reduction of MAS in the spinal cord origin group was 2.6 (mean, 3.5 to 0.9), cerebral origin group was 2.9 (mean, 3.3 to 0.4), and other origin group was 2.5 (mean, 3.6 to 1.1). The change in MAS was not significantly associated with diagnostic group (Pearson chi-square 7.458, p = 0.488) (Fig. 1). However, there was a statistically significant, negative correlation

Table 1
Demographic and complication data.

Demographics & Complications			
Demographic data			
Sex	Male (55)	Female (33)	
Age at implant (mean)	44.2 years (range 19-71)		
Antispasmodic meds at time of implant	Yes (82)	No (6)	
ITB Test dose[^]	50 mcg (78)	100 mcg (1)	Not documented (9)
Participants	88 total		
Classification[*]	Spinal cord origin (40)	Cerebral origin (8)	Other origin (40)
Complications in the perioperative period after IDD implant (0-24 months)			
PDPH[#]	Yes (20)	No (64)	Not documented (4)
Infection	Yes (3)	No (80)	Not documented (5)
Pump malfunction	Yes (3)	No (78)	Not documented (7)
Catheter malfunction	Yes (16)	No (65)	Not documented (7)

[^]ITB – Intrathecal baclofen.
[*]Spinal cord origin – spinal cord injury from traumatic and non-traumatic events.
Cerebral origin – cerebral injury from cerebral palsy, stroke, TBI.
Other origin – upper motor dysfunction from multiple sclerosis, spastic paraparesis, etc.
[#]PDPH – post-dural puncture headache.