IT Baclofen Drug Distribution Pilot Study: Proposal to Medtronic

Goal:

While ITB therapy is commonly recommended for treatment of severe spasticity due to a variety of diseases, the location of optimal drug (baclofen) delivery has not been defined in a controlled study. Furthermore, the cost of pharmacological management in these patients is significant, and optimal location for drug delivery through an implantable drug pump may have significant impact on the cost burden of maintenance refills. It is the goal of this pilot study to determine whether there is a significant therapeutic advantage to place the ITB catheter within the cervical, thoracic or lumbar region of the spine. It is also a goal of this pilot study to determine whether the origin of spasticity influences the effect of Lioresal Intrathecal (baclofen injection) on ITB catheters located in the cervical, thoracic or lumbar regions of the spine. We propose to study the impact of catheter location on the reduction in spasticity within a group of patients who are scheduled for ITB trial. Furthermore, we intend to enroll patients whose spasticity originates from two different mechanisms (SCI causing spastic paraplegia vs. cerebral palsy causing spastic spasticity of spinal and cerebral origin. In studying the impact of catheter location among patients with spinal versus cerebral origin of spasticity, the disease origin may also have a significant impact on baclofen dosing relative to the placement of the catheter.

In addition, the pharmacokinetic half-life and the variability of intrathecal baclofen is poorly understood as data is limited. In order to provide initial data regarding CSF baclofen washout, samples of spinal fluid obtained just prior to- and following IT baclofen administration will be obtained for delayed analysis. The results of these pharmacological analysis may refine the understanding of how quickly baclofen is distributed from a given catheter location, and whether it is affected by catheter location or disease origin. Since multiple catheter locations will be studied within a given patient, it also affords the opportunity to sample small amounts of CSF at key anatomical sites along the spinal axis as an independent secondary study protocol.

Hypotheses:

- Ho_1: There is no significant ($p > 0.05$) difference in clinical spasticity (as measured by using the Modified Ashworth Spasm Rating Score) when the same amount of baclofen is delivered (50µg) to the cervical, thoracic, or lumbar area on separate days.
- Ho_2: There is no significant ($p > 0.05$) difference in the response to Lioresal Intrathecal (baclofen injection) between patients with spinal versus cerebral origin of spasticity relative to catheter tip placement.

Specific Aims:

1. Measure the degree of spasticity based on the Modified Ashworth Scale for Grading Spasticity in patients undergoing daily, single ITB bolus injections through an intrathecal catheter located in the mid-cervical (C4), mid-thoracic (T3), thoraco-lumbar (T10) and upper lumbar (L2) regions.
2. Measure the Spasm Rating of patients undergoing daily, single ITB bolus injections through an intrathecal catheter located in the mid-cervical (C4), mid-thoracic (T3), thoraco-lumbar (T10) and upper lumbar (L2) regions.

3. Sample CSF at each of the catheter tip locations just prior to ITB injection. Sample CSF at 1, 5, 10, 20, 60 min following ITB administration.
4. Each subject will receive prophylactic antibiotics for the duration of the IT catheter placement.

Methods:

Subjects who have spasticity and have consented for a trial of ITB therapy as part of a normal therapeutic evaluation, will be asked to enroll in this study. As a pilot study, we are interested in observing significant changes ($p< 0.05$) in either Ashworth Rigidity or Spasm scores related to catheter tip location along the spinal axis. Each subject will serve as their own control and will be assessed by the same rater throughout the study. The subjects will initially undergo temporary implantation of an intrathecal catheter placed under sedation or light anesthesia with fluoroscopic guidance. This will be done by the neurosurgeon with the intent of positioning the catheter initially in the mid-cervical region (C4) of the spine. The following day, after sedation / anesthetic effects are worn off, the subject will undergo a spasticity evaluation in the morning prior to ITB injection (See Tables 2 and 3 regarding Modified Ashworth and Spasm rating scores). Then a 50 microgram (μg) dose of IT baclofen will be injected into the CSF through the catheter. Samples of CSF (3cc) will be withdrawn from the IT catheter just prior to injection and at 10, 30, 60, 120, and 360 min following the ITB injection. The rater (Nurse Practitioner) will perform an Ashworth and Spasm rating exam on the subject at 2, 4, and 6 hours following the ITB injection. Each subject will be allowed to recover and observed overnight in the Clinical Research Center (CRC) at Vanderbilt University.

The following morning, each subject will be brought to the radiology department fluoroscopy room and the IT catheter withdrawn to the next lower level being studied – viz. T3, T10, or L2. Catheter position prior to- and after repositioning will be documented on digital radiograph. The subjects will then be returned to the CRC area and dosed with IT baclofen (50 micrograms IT baclofen). The same protocol for assessing spasticity (Ashworth score) and spasms (Spasm rating) will be performed that day associated with the new catheter position. In other words, a spasticity assessment will be performed just prior to injection, and at 2 hour intervals following injection up to 6 hours after injection. Likewise, a CSF sample will be withdrawn just prior to injection, and at logarithmic intervals up to 6 hours following injection. Each CSF sample will be no more than 3 cc and must represent a clean sample of CSF from the subject.

At the end of the fifth day of study, the IT catheter will be withdrawn and a stitch placed over the hole in the skin. The subject will be allowed to stay overnight for observation and then released the following morning. Implantation of the ITB pump will be determined as usual by the implanting neurosurgeon and his staff (*note: The decision as to whether the subject or the clinical team decides to implant an ITB pump is outside the scope of this project, and would be considered part of their routine medical care following the trial of ITB).*

Selection of subjects. We will attempt to enroll ten subjects for each disease category by the end of two years. A total of 20 subjects would be enrolled to complete this study. We wish to enroll subjects with similar mechanisms of spasticity for each disease category. Our initial disease categories will involve subjects who have spasticity from very different mechanisms to determine if ITB dosing is significantly different due to origin of spasticity. One group of subjects would have spasticity due to spinal cord injury and are paraplegic, thereby recognizing that their spasticity originates from the lower half of the spinal cord in general. Another group of subjects would have spasticity due to cerebral palsy and are

quadriparetic, thereby recognizing that their spasticity originates from loss of upper motor neurons as a result of cerebral disease (typically associated with a perinatal infarct). Other disease categories, such as cervical spine SCI, stroke, hereditary spastic paraparesis, multiple sclerosis, can be considered in the future if a significant difference ($p < 0.05$ on ANOVA analysis) exists between the two broad categories represented in this pilot study.

There may be reasons why subjects may not be able to complete the study. Some foreseeable reasons include:

- Intradural blockage that prevents advancing the IT catheter to the level of C4, verified by a total MRI of the spine (Cervical, Thoracic, and Lumbar levels), without contrast injectyion, sagittal views only.
- Significant left over effect of the previous day's administration of IT baclofen thereby prevent a detectable change in spasticity in subsequent injections
- Allergic reaction to IT baclofen
- Withdrawal of the subject from the study
- IT catheter malfunction
- Significant headache from CSF withdrawal
- CSF leak that is intolerable (headache or otherwise) from the IT catheter entry site

Results Anticipated:

The data will be collected according to the following schedule per patient.

Table 1. Study variables and the timing of data collection. Each table is for a specific catheter location within a given patient. This table, for example, would be filled out 4 times corresponding to the four different catheter locations studied each day.

Time	Catheter Location	Modified Ashworth Score	Spasm Score	CSF Sample
Baseline	C4, T3, T10, L2	0-4	0-4	3cc
Injection (50µg)	-	-	-	-
1 min	-	-	-	3cc
2 min	-	-	-	3cc
10 min	-	-	-	3cc
20 min	-	-	-	3cc
60 min	-	-	-	3cc
2 hours (120min)	-	0-4	0-4	-
4 hours (240 min)	-	0-4	0-4	-
6 hours (360 min)	-	0-4	0-4	-
Total				18 cc / day

Table 2. Modified Ashworth Scale for Grading Spasticity

Grade	Clinical Rating of Tone
0	No increase in tone
1	Slight increase in muscle tone, manifested by a catch and release, or by minimal resistance at the end of the range of motion when the affected

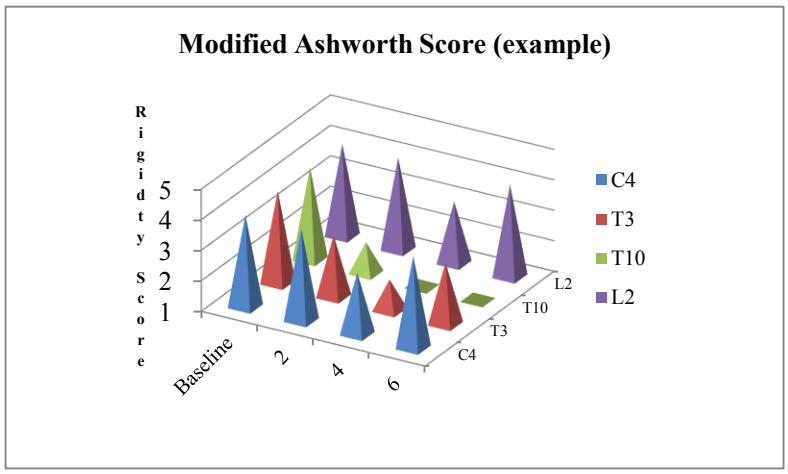
	part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

Table 3. Penn Spasm Frequency Scale

Spasm Score	Spasm Frequency
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**

Spasm Severity	Severity Rating
1	**Mild**
2	**Moderate**
3	**Severe**

For a given subject, the data will be analyzed for the following effects:



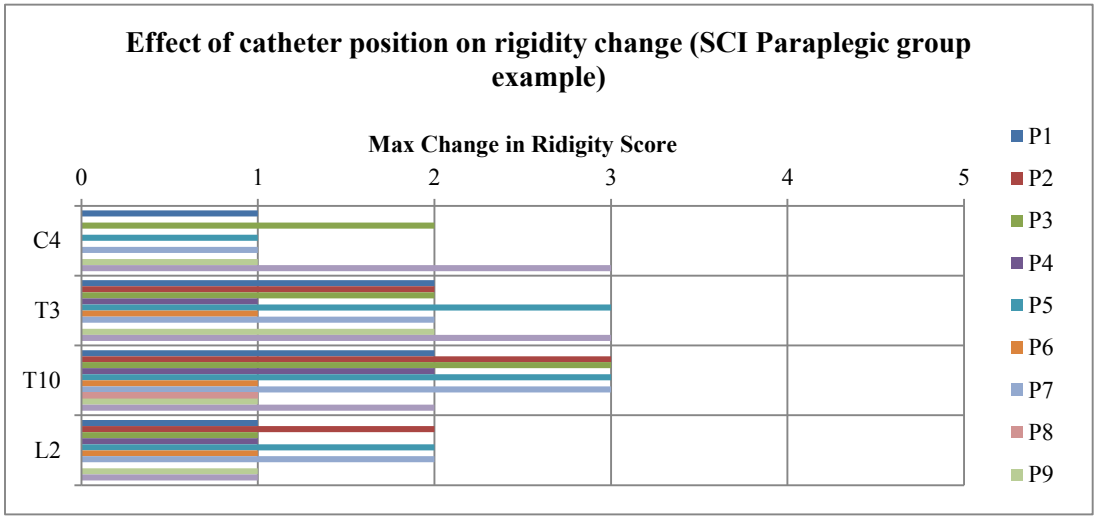
1. What was the effect of identical baclofen doses (50µg) administered at different spinal levels within each subject on rigidity? (expect reduction in score over 4-6 hours with possible return towards baseline at 6-10 hours)
2. What was the effect of identical baclofen doses (50µg) administered at different spinal levels within each subject on spasms? (expect reduction in score over 4-6 with possible return towards baseline at 6-10 hours)
3. Is there a significant difference in location of the catheter on the maximum reduction in either spasticity or spasm scores? (expect this to show as the largest "dip" in scores on 3D graph)
4. Is there a "washout" effect from day to day? (if so, expect the baseline scores to be lower each day) If present, this would suggest that the daily dosing is too high.

For each group (SCI vs CP), the data will be analyzed as follows:

1. What catheter location caused the greatest change in spasticity scores? (the location of the catheter – C4, T3, T10 or L2 – would be noted and averaged among the ten subjects). Expect that

SCI group would favor greater change when catheter is located at T10 or L2. Expect that CP group might not show a significant difference in catheter location.

2. What catheter location caused the greatest change in spasm scores? (the location of the catheter – C4, T3, T10 or L2 – would be noted and averaged among the ten subjects) Expect that SCI group would favor greater change when the catheter is located at T10 or L2. Expect that the CP group would not have much spasm change based on catheter location.



Parameter	SCI Paraplegic (n=10)	CP Quadriparetic (n=10)
Greatest change in Ashworth Score vs Location	? ANOVA	? ANOVA
Greatest change in Spasm Rating vs Location	? ANOVA	? ANOVA
Difference in Ashworth Score between days (assess washout effect)		

Subject Recruitment and Length of Study:

We expected to be able to recruit 20 patients for this study within two years. The subjects would be solely recruited and managed through the Adult Neurosurgery practice at Vanderbilt. Patients would be approached for enrollment after first choosing to undergo an ITB trial for the treatment of their spasticity.

Procedure/Activity	Frequency
Patient consent	Clinic visit 1 1
MRI Total Spine without contrast	Outpatient Radiology 1
Implantation of intrathecal catheter under light sedation and fluoroscopy guidance to C4	Inpatient MCE Day 1 1 Transfer to CRC after wake-up from MCE procedure (CRC Day 1)
Baclofen Injection (50μg)	Inpatient CRC Day 2
Modified Ashworth Rigidity testing and Spasm rating	Inpatient CRC Day 2 at 2, 4, and 6 hours following injection
CSF Specimen 3cc	Inpatient CRC Day 2 10 min, 30 min, 60 min, 120 min, 360 min
Repositioning of intrathecal catheter to next lower level or T3 under fluoroscopy	Inpatient Radiology Day 3 1 (for this day)
Baclofen Injection (50μg)	Inpatient, CRC, Day 3
Modified Ashworth Rigidity testing and Spasm rating	Inpatient, CRC Day 3 at 2, 4, and 6 hours following injection
CSF Specimen 3cc	Inpatient CRC Day 3 10 min, 30 min, 60 min, 120 min, 360 min
Repositioning of intrathecal catheter to next lower level or T10 under fluoroscopy	Inpatient Radiology Day 4 1 (for this day)
Baclofen Injection (50μg)	Inpatient CRC Day 4
Modified Ashworth Rigidity testing and Spasm rating	Inpatient CRC Day 4 at 2, 4, and 6 hours following injection,
CSF Specimen 3cc	Inpatient CRC Day 4 10 min, 30 min, 60 min, 120 min, 360 min

Repositioning of intrathecal catheter to next lower level or L2 under fluoroscopy	Inpatient Radiology Day 5	1 (for this day)
Baclofen Injection (50μg)	Inpatient CRC Day 5	
Modified Ashworth Rigidity testing and Spasm rating	Inpatient CRC Day 5 at 2, 4, and 6 hours following injection	
CSF Specimen 3cc	Inpatient CRC Day 5 10 min, 30 min, 60 min, 120 min, 360 min	
Catheter withdrawal	Inpatient CRC, Day 5	
Discharge	Inpatient, CRC, Day 6	