Cover Page

Study title: “Effectiveness of Self-Administered Boluses of Intrathecal Bupivacaine in Patients with Chronic Non-Cancer Pain Implanted with IDDS: A Double Blind Randomized Study”

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Department of Anesthesiology
Division of Pain Medicine
Study title: *"Effectiveness of Self-Administered Boluses of Intrathecal Bupivacaine in Patients with Chronic Non-Cancer Pain Implanted with IDDS: A Double Blind Randomized Study"*
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Protocol Title:
"Randomized, double blind, cross over study comparing effectiveness of traditional opioids versus opioids in admixture with bupivacaine upon self-administration of boluses via a Personal Therapy Manager (PTM) in Intrathecal pump".

ABSTRACT

2.1 Purpose:
To determine whether the local anesthetic bupivacaine delivered intrathecally in small doses via PTM self-administered boluses significantly improves the breakthrough pain and functional status of patients with chronic intractable pain who are managed with an intrathecal drug delivery system.

2.2 Research Design:
Randomized, double-blind cross over effectiveness study.

2.3 Methodology /Technical Approach:
Seventeen patients who are already using SynchroMed II pump containing an admixture of bupivacaine and an opioid and using PTM doses will be randomized into two groups:
Group I: Will have the intrathecal pumps refilled with 10 milliliters of a solution containing their usual intrathecal opioid with bupivacaine.
Group II: IT pump will be filled with 10 ml of intrathecal opioid without bupivacaine.

Both patients and the evaluating physician will be blinded.

In order to accomplish this, only the central compounding (investigational) pharmacy at University Hospitals Case Medical Center would make two solutions labeled: A or B respectively. Study subjects will be randomized and randomization order will be held at the pharmacy that will supply the medication. Patients will be kept on each solution for one week. Data will be collected daily.

3. OBJECTIVESAND RATIONALE

The objective of this project is to conduct a randomized, double-blind, effectiveness study to determine whether intrathecal delivery of bupivacaine via self-administered boluses significantly improves breakthrough pain and functional status in patients with chronic, non-cancer pain who are managed with an implanted intrathecal drug delivery system (IDDS). This is important because some practitioners choose only a mono therapy (i.e. opioid) in the intrathecal solution without bupivacaine. This would delay pain relief without the near instant relief bupivacaine has been reported to provide after a PTM bolus.

4. MEDICAL APPLICATION

Intrathecal drug delivery is an established interventional modality in managing different chronic pain conditions, especially post laminectomy syndrome, also known as failed back surgery syndrome (FBSS). Intrathecal delivery of pharmacological agents reduces systemic side effects and the potential for aberrant medication use[1].

Previous publications from our center have demonstrated that bupivacaine in combination with intrathecal opioids results in long term relief and reduces opioid dose escalation[2]—an important problem in intrathecal drug delivery Particularly, the PTM dosing function with bupivacaine has rapid onset of action[3] (given bupivacaine site of action preferentially on nerve rootlets) which significantly improves patient satisfaction[4].

5. BACKGROUND AND SIGNIFICANCE

Treatment of chronic pain is a challenging endeavor and intrathecal drug delivery is an important tool in the armamentarium of Pain Medicine specialists.

Continuous intrathecal drug delivery is an interventional modality often applied in refractory chronic pain of cancer or non-cancer etiology. Intrathecal drug delivery systems (IDDS's) involve programmable pumps that constantly deliver the medication into the spinal canal but also may allow the patients to self-administer a dosage of medication that is pre-determined by the clinician in terms of dose and frequency. The use of this latter feature helps control emergent (breakthrough) pain and/or preempts predictable mechanical pain. The patient is provided with a remote control device (called Personal Therapy Manager—PTM) that is easy to use and allows self-administration of boluses[3,4].

Standard of care medications used in IDDS include opioids such as morphine or hydromorphone and the local anesthetic bupivacaine. A combination of an opioid with bupivacaine is used in the vast majority of patients implanted at University Hospitals Case Medical Center.

Opioid medications work by binding to opioid receptors in the substantia gelatinosa in the dorsal horn of the spinal cord. Hence, the opioid would have to diffuse 1-2 mm below the surface of the spinal cord in order to reach its target and effect pain relief. Similar to other local anesthetics, bupivacaine works by blocking sodium channels. While these are distributed ubiquitously in the nervous system, it is much more efficient for bupivacaine to bind to sodium channels on nerve rootlets (fila radicularia or small branches that divide off each nerve root before it plugs into the cord). This may explain why many patients

who use a PTM to self-administer boluses report instant pain relief when bupivacaine is present in the intrathecal pump solution[1].

The effective analgesic PTM dose of bupivacaine is 0.4-1.5 mg and is self-administered with a lock-out interval of 15-120 minutes as needed for pain control. The dose is titrated for analgesic effectiveness without causing motor impairment.

6. PLAN

6.1 New Investigational Drugs/ Investigational Devices Exemption Status: N/A

6.2 Selection of Subjects

6.2.1 Type of the Subject Population

Patients with intractable chronic pain being managed with an intrathecal drug delivery system programmed with a continuous infusion as well as a self-administered bolus (PTM) for breakthrough pain who have an opioid as well as bupivacaine in the intrathecal solution and have been stable on their current settings for at least 3 months.

6.2.2 Inclusion and Exclusion Criteria

a. Inclusion Criteria

- Age more than 30 years implanted with an intrathecal drug delivery device.
- Intrathecal pump patients on stable dose for the last 3 months.
- Using on average more than 2 and less than 10 PTM doses per day
- Intrathecal medication admixture consisting of bupivacaine and another opioid (fentanyl or hydromorphone or morphine)

b. Exclusion Criteria

- Using 10 or more PTM bolus doses per day or 2 or less PTM bolus doses per day
- Pending litigation or worker compensation claim
- Any recent (less than 3 month) procedures in spine (surgeries) or catheter adjustments.
- Recent pump dose adjustment within the past 3 months
- Pumps with medications other than bupivacaine opioid combination.

6.2.3 Recruitment

Subjects will be recruited from among patients seen at the University Hospitals pain clinic at UHCMC by attending physicians. Screening will be done before obtaining consent by an investigator. Screening for stable programmed mode and dose of medication for at least

three months. Except for parking pass and meal pass, no subject will be compensated for participation.

6.2.4 Consent Process

The Principal Investigator and/ or associate investigators will present and explain in detail the consent and HIPAA authorization forms to potential participants. If interested, eligible individuals will be given the opportunity to ask and have all questions answered before signing the informed consent document and HIPAA authorization form.

Subjects will be consented by one of the investigators after they are screened by a pain clinic attending for eligibility, before having their intrathecal drug delivery system refilled. In subjects who elect to participate, the consent form will be taken home to be examined and after a detailed explanation is given, will be signed in the clinic during the next visit for the refill. An explanation in lay terms for the reason of the study and the proposed effectiveness bupivacaine has on near immediate relief of breakthrough pain will be used to promote patient understanding.

6.3 Study Design and Methodology

6.3.1 Study Design

This is a randomized, double-blind, effectiveness study looking at self-administered boluses of an opioid with and without bupivacaine via a Personal Therapy Manager (PTM) in patients with an intrathecal drug delivery system to assess the effect of bupivacaine administered by PTM on pain scores and functional status in patients with breakthrough pain. Patients in group I will receive a refill of a 10 mL solution "A" containing their usual intrathecal opioid and including bupivacaine. Patients in group II will receive a refill of a 10 mL solution "B" containing their usual intrathecal opioid without bupivacaine. Both groups will be kept on solution A and on solution B for a maximum of one week each after which they will cross over to the other solution for one week and then exit the study. The patients will then be returned to their baseline programming. Potential changes in programming to benefit patients may be undertaken as necessary—if existent--after unblinding. Primary outcome measures will include 0-10 numerical rating scale (NRS) or Visual Analogue Scale (VAS) both immediately before and within 30 minutes after a PTM bolus. Patients will be provided with a diary to record pain scores just before a PTM bolus and the lowest pain score within half an hour after a PTM bolus. Only 5 recording per day will be available on the diary—thus patients would record pain scores only before and after the first 5 PTM boluses. However, the scores before and after the first 3 successful PTM boluses would be the only ones considered. Successful PTM activations would be determined by review of the patient PTM diary and the internal log from the intrathecal drug delivery system. Each recording on the PTM diary would be time matched to the successful PTM activation code in the internal log. This will obviate any potential mis-administered bolus whereby the patient does not activate the bolus device appropriately.

Secondary outcome measures will include average NRS pain scores for the day, functional capacity as evaluated by the Oswestry disability index (ODI) scores, number of boluses used, paresthetic sensation post bolus, and Global Perceived Effect.

6.3.2 Study Methodology/Procedures

Seventeen patients who are already using Intrathecal therapy and PTM dose will be randomized in a 1:1 ratio by a computer generated randomization table to receive one of two treatments. At patient's regular scheduled appointment for pump refill, the residual intrathecal medication volume will be removed from the pump and half of the patients will be allocated to receive the opioid alone whereas the other half will receive the same solution containing the opioid with bupivacaine.

At each of the first two visits following signing of informed consent Patient should be refilled in the IDD pumps with a 10 mL solution containing either the usual intrathecal medications (solution A or Solution B–coded by pharmacy) including bupivacaine with the opioid (same intrathecal solution) or their usual intrathecal solution with the same opioid concentration but without bupivacaine. Taking away bupivacaine from the intrathecal solution does not result in withdrawal. The investigational pharmacy at UHCMC would be the only party who knows whether the patients are receiving solution A or solution B. No changes will be recorded in pump programming with respect to the opioid. However, upon each of the two first visits after consent, when the patients are refilled with 10 ml of solution A or solution B, the pump will be programmed with the same concentration of the opioid and bupivacaine labeled at 29 mg/ml at the first visit and 30 mg/ml at the second visit. Changing the solution at the first visit to a label of bupivacaine 29 mg/ml will not affect the delivery of the opioid or bupivacaine (if the solution has bupivacaine) as the only (and primary) driver for amount delivered is the opioid which will not change in concentration or dose throughout the study. However, labeling the bupivacaine with 29 mg/ml (a concentration not used and different from previous bupivacaine concentration) will prompt the decision algorithm to request a "bridge bolus"—namely, a calculation of how long it would take for the new solution to get through the dead space in the pump and catheter to get to the catheter tip. Upon changing the solution in the pump, it may take about a day or so for the new medication to enter the intrathecal space because of dead space. The exact duration is dependent on the patient's initial rate (ml/day) the length of the catheter in the patient; thus would vary from patient to patient. The dead space in the Medtronic SynchroMed II pump is comprised of the internal tubing within the pump (0.199 ml) + external catheter tubing extending from the pump to the Intrathecal space (usually about 0.1 to 0.15 ml). This amount is calculated at pump change and is usually on the order of one day, but varies and the pump programmer will calculate the exact date when the bridge bolus is completely delivered. Importantly, during the bridge bolus, the patients will not be able to self-administer PTM boluses. Many patients may be used to this with solution changes. When the bridge bolus is completely administered, usually after a day or so, the

patient will be able to self0-administer PTM doses. When doing so, the patients will be receiving either opioid + bupivacaine (exactly similar to baseline) or opioid alone (similar

to baseline but without bupivacaine). Hence, patients will continue to have access to PRN (as necessary) analgesia with self-administered PTM doses. As patients will be kept on solution A or solution B for a maximum of one week each, the maximal duration without bupivacaine in the intrathecal bolus would be one week.

The patients will be provided with a paper diary that will be attached by Velcro to the PTM remote device which will act as a reminder for patients to record pain scores prior to the PTM bolus. The patients will also record the lowest pain scores within the first 30 minutes after a PTM bolus. Only the first 3 successful PTM boluses per day will be recorded and tracked by the study. The patients will also record the average NRS score and GPE score daily. Reminders to complete the diary will also be provided to patients via phone, email or text message.

6.3.3 Collection of the Human Biological Specimens: N/A6.3.4 Data Collection

Randomization will be performed, patients will be recording data and baseline data will be collected during the first day or so after refilling with the study solution and the study data over the ensuing few days. No programming changes will be made during the study period. All participants will be kept on solution "A" and solution "B" for a maximum of one week each. All data will be obtained by a physician or member of the research staff.

6.3.5 Study Time Line

Assessment	**4-8 wks before rx**	**1-2wks before**	**1st refill Time 0**	**1 week later 2nd refill**	**2 weeks**	
Screening and Informed conse	x					
Randomization/data collection Questionnaire administration		x				
Initial study visit			x			
1st follow-up Data collection Including questionnaires				x		
2nd follow up Data collection for 2nd week					x	

6.4.1 The primary endpoints (i.e., primary outcome variables) and the secondary endpoints, if any.

The primary outcome variable will be the average change in the NRS for back pain scores between NRS scores before PTM bolus and NRS scores within 30 minutes after PTM bolus. Secondary outcome variables will be Oswestry disability score, satisfaction (categorical "positive" or negative"), the Global Perceived Effect score and side effects (medications). These variables will be recorded at baseline and during each follow-up visit. Global Perceived Effect and Oswestry questionnaires (as well as adverse effects) will be collected at baseline and at the end of each one-week study period.

6.4.2-3 Data analysis, interim analysis and stopping rules

Baseline data will be compared using analysis of variance (parametric or Kruskal Wallis ANOVA) for continuous or ordinal data and the chi square test for categorical data.

6.4.4 Sample Size Estimation

To estimate the sample size we based our calculation on the primary outcome which would be:

A. The difference of the average of the change in pain intensity score [Avg D NRS] of the first 3 successful PTM daily for 5 days [maximum 15 PTM boluses] between the Group I and Group II.

Specifically, from the literature and previous experience usually a change of 2 points in absolute pain score is considered minimally clinically significant. The provided parameters were: significance level (adjusted for sidedness) = 0.05, standard deviation within patients = 2, standard deviation of the difference = undefined, number of patients = undefined, power = 0.8, difference in means = 2.

The variable calculated was the total number of patients.

A total of 14 patients will enter this two-treatment crossover study. The probability is 80 percent that the study will detect a treatment difference at a two-sided 0.1 significance level, if the true difference between treatments is 2 points [NRS]. This is based on the assumption that the within-patient standard deviation of the response variable is 2.

Another 10-20% (or up to 3 patients should be factored in the sample size to account for normal withdrawals from the study. ***The final number of patient to be recruited for this study would be 17.*** These calculations were made using the sample size software.

6.5 Reporting Adverse Events

6.5.1 Expected Adverse Events from Research Risks and Reporting

Adverse effects are not expected from this minimal intervention. All precautions would be taken to do the pump refills in the aseptic manner. Other possible side effect would be poor pain control.

All investigators will take the same steps normally taken to minimize adverse events.

6.5.2 Reporting Serious and Unexpected Adverse Events to the IRB

Serious Adverse Events: The PI, within one working day, will report all serious adverse events (SAE) occurring in any subject. This will be accomplished by submitting an adverse event report memorandum to the IRB.

Unexpected (but not serious) adverse events which, in the opinion of the PI, are possibly related to participation in the protocol will be reported by the PI within 10 (ten) working days to the IRB using the same procedure.

For all serious and/or unexpected adverse events, the PI will examine the adverse event for relation to the study (unlikely given the study is examining the effect of removing the local anesthetic from the intrathecal solution—not adding any new drugs) and report if needed to the IRB.

6.6 Banking of Human Biological Specimens/Tissue (HBS/tissue): N/A

***6.7 Subject Confidentiality Protection:** All treatments received in this study are standard of care. No data will be collected that is not relevant to patient care (e.g. treatment, analgesic usage, numerical rating scale pain scores and disability scores), and no data will be shared with any non-investigator. In addition to name and date of birth, patients will also identified by their place on the randomization table (e.g. RT 2, PT 3). This "code" will enable the transfer of study information without mentioning patients' names

6.7.1 Certificate of Confidentiality: N/A

***6.7.2 HIPAA Authorization**

i. Are you intending to collect subject's Protected Health Information (PHI) and any of the following 18 personal identifiers?

___ No – HIPAA does not apply – go to question #**iv**
_x__ Yes – please check which ones:
___ 1. Names
___ 2. Street address, city, county, 5-digit zip code

_x__ 3. Months and dates (years are OK) and ages >89 (unless all persons over 89 years are aggregated into a single category)
_x__ 4. Telephone numbers
_x__ 5. Fax numbers
_x__ 6. E-mail addresses
___ 7. Social security number
___ 8. Medical record number
___ 9. Health plan beneficiary number
___ 10. Account number
___ 11. Certificate/license number
___ 12. Vehicle identification number (VIN) and/or license plate number
___ 13. Device identifiers and serial numbers
___ 14. URLs (Uniform Resource Locators)
___ 15. Internet protocol address number
___ 16. Biometric identifiers, such as finger and voice prints
___ 17. Full face photographic images or any comparable images
___ 18. Any other unique identifying number, characteristic, or code such as patient initials

ii. Can you limit your collection of personal identifiers to just dates, city/state/zip, and/or "other unique identifier" (#18 of the above)?
___ Yes – then your dataset may qualify as a Limited Data Set – please complete a Data Use Agreement and attach to your protocol. Then go to question #**iv**.
_x__ No – Go to question #**iii.**

iii. Is obtaining patient Authorization "impracticable"?
___ Yes – Authorization may qualify to be waived by the IRB. Go to *Section 6.7.3* HIPAA Authorization Waiver for the application.
_x__ No – Research subjects will need to sign a HIPAA Authorization. Complete the HIPAA Authorization and attach to this protocol.

iv. What precautions will you take to protect the confidentiality of research source documents (Case Report Forms, questionnaires, etc.), the research data file, and the master code (if any)?

A randomization table will be developed by a computer generated random number sequence. This "code" and a copy of all data collection sheets will be kept by our research staff in a locked office and protected by computer passwords as well as the UHCMC compounding pharmacy that will prepare the solutions labeled as described.

v. When will you destroy the research source documents, data file, and the master

code?

The UHCMC research team in the Pain Medicine Clinic will keep the research data for up to six years after the end of the study. Then all the information will be destroyed. The master code will be destroyed as soon as all data collection is completed.

vi. Will research data including Identifiable Protected Health Information be sent outside of UHCMC? No

6.7.3 HIPAA Authorization Waiver: N/A- We will obtain signed HIPAA authorization from each patient.

6.8 Reporting Protocol Deviations

Minor protocol deviations (e.g. minor changes in the consent process, prolonged completion time due to deployments) will be discussed with the investigative team on a standard protocol deviation sheet.

1. Hayek SM, Hanes MC. Intrathecal therapy for chronic pain: current trends and future needs. *Current pain and headache reports.* Jan 2014;18(1):388.
2. Veizi IE, Hayek SM, Narouze S, Pope JE, Mekhail N. Combination of intrathecal opioids with bupivacaine attenuates opioid dose escalation in chronic noncancer pain patients. *Pain Med.* Oct 2011;12(10):1481-1489.
3. Hayek SM, Veizi E, Hanes M. Intrathecal Hydromorphone and Bupivacaine Combination Therapy for Post-Laminectomy Syndrome Optimized with Patient-Activated Bolus Device. *Pain Med.* Dec 14 2015.
4. Ilias W, le Polain B, Buchser E, Demartini L. Patient-controlled analgesia in chronic pain patients: experience with a new device designed to be used with implanted programmable pumps. *Pain practice : the official journal of World Institute of Pain.* May-Jun 2008;8(3):164-170.