Dose Escalation of Dexamethasone to Increase Duration of Transversus Abdominal Plane Block Following Cesarean Section

Study Protocol and Statistical Analysis Plan

NCT03098420

July 22, 2016

Joel Feinstein, MD, Principal Investigator
University of Alabama at Birmingham
Birmingham, AL 35294

Dose Escalation of Dexamethasone to Increase Duration of Transversus Abdominal Plane Block Following Cesarean Section. A Prospective Randomized Double-Blinded Clinical Study.

Principal Investigator: Joel Feinstein, M.D.
Co-Investigators: Timothy Torres, M.D.; William Potter, M.D.;
Promil Kukreja, M.D., Ph.D.; Timothy Ness, M.D.;
Stacy Wade, M.D.
Clinical Research Coordinators:

Version Date: 03/03/2016
IRB Study Number: XXXXXXX

INDEX

1.0 SUMMARY OF STUDY (Abstract with a maximum of 300 words)

Postoperative pain is a cause of great angst among patients undergoing surgical procedures, and many patients voice concerns over anesthesia and postoperative pain as much as their actual surgical procedures. These sentiments are no different in the obstetric population planning to endure cesarean section.

As there are growing pressures to improve postoperative pain while decreasing opioid consumption, there have been few substantial changes to post cesarean section pain management techniques in recent years; however, several studies have shown potential benefit for the use of transversus abdominal plane (TAP) blocks to decrease post-surgical pain, as well as minimize opioid usage. The potential benefits of TAP blocks are extensive, while the risks associated with the procedure are relatively minimal, and unlike continuation of an epidural catheter, the TAP block should not show the potential negative effects of lower extremity numbness/weakness, bladder/bowel dysfunction, epidural abscess/hematoma, or coagulation monitoring.

The use of only local anesthetic for this fascial plane abdominal block may not have wide use in this field due to its minimal duration of action after the cessation of neuraxial anesthetic, but if the duration of action could be substantially extended, this technique may become a more common practice to improve patient care and satisfaction.

When combined with local anesthetic in TAP blocks, dexamethasone has the potential to prolong the duration of analgesia following cesarean section. Dexamethasone is well-known for its anti-emetic and anti-inflammatory properties; however, it has also been shown in studies to reduce post-operative pain and increase the duration of regional anesthesia blocks. The dosage required to show significant benefit, however, has not been established with any consistency.

Our study aims to determine if and at what dose does dexamethasone consistently extend the duration of these blocks; thereby, improving post-cesarean section pain.

2.0 BACKGROUND & RATIONALE

Recent studies have analyzed the efficacy of TAP blocks for post-surgical analgesia following abdominal procedures, including cesarean sections, with many of these studies showing superior analgesia when compared with infiltrative anesthesia and intravenous post-operative opioids alone (1-5), and they have shown minimal risk to the patients.

Dexamethasone as well has been studied and has shown in several trials to not only help reduce PONV but also to decrease post-cesarean pain in the first 48 hours. A dose of 5mg of dexamethasone has been suggested to be the minimum amount required to achieve the desired results with intravenous medication use (6).

There have been several studies looking at the potential benefits of utilizing dexamethasone as an adjuvant in regional anesthetic blocks to prolong duration of block and subsequently to provide superior post-operative analgesia with minimal side effects (8, 9);

however, there is minimal data on its role and dosage as an adjuvant to TAP blocks following cesarean section (7).

Our study hopes to show that the addition of dexamethasone in bilateral TAP blocks will prolong the duration of the block in a dose-dependent fashion. We will also analyze this data to attempt to show that the prolongation of the block will also decrease post-operative pain, decrease opioid consumption, and improve overall patient satisfaction.

3.0 SIGNIFICANCE OF STUDY

Our study aims to improve the care of the obstetric population after cesarean section and improve total patient satisfaction by improving post-surgical pain control with the use of dexamethasone in combination with bilateral TAP blocks. We will utilize a dose-escalation of dexamethasone in the TAP block to observe its effects at specific small doses. Our hope is that our technique would become utilized routinely for the obstetric population following cesarean section.

4.0 OBJECTIVE(S) & HYPOTHESIS

Purpose: improve post-operative pain following cesarean section, increase duration of TAP block with use of dexamethasone, decrease overall pain scores in the first 24-48 hours, and decrease opioid requirements after cesarean section.

Outline of Therapy:

Primary endpoints or outcomes:

1. Estimation of duration of TAP block, assessed within 48 hours after surgery

Secondary endpoints or outcomes:

1. Pain scores (VAS) at immediate post-op, every 15 minutes in the PACU, then every 6 hours on an inpatient floor until approximately 48 hours post-operatively.
2. Average pain score in first 48 hours
3. Time until first dose post-operative opioid administration
4. Opioid consumption in first 48 hours post-operatively
5. Use of rescue PONV medications (i.e. ondansetron, promethazine)
6. Patient satisfaction

Study Hypothesis: Dexamethasone will demonstrate a significant increase in duration of TAP block in a dose-dependent fashion when compared with local anesthetic alone.

5.0 INTERPRETATION OF EXPECTED RESULTS

We expect our results to confirm our hypothesis that post-operative bilateral TAP blocks with dexamethasone will show a significant increase in duration of TAP block in a dose-dependent fashion; thus it will show an overall improvement in post-operative pain in the first 48 hours following cesarean section.

6.0 ELIGIBILITY & EXCLUSION CRITERIA

Eligibility criteria:

1. Women, 18 years and older, undergoing elective cesarean section delivery.
2. Patients classified as American Society of Anesthesiology class II or III.
3. Spinal anesthesia utilized as intra-operative anesthesia for cesarean section.

Exclusion criteria:

1. Any patient not classified as an ASA II or III.
2. General Anesthesia or neuraxial anesthesia with epidural used as anesthetic techniques for cesarean section.
3. Emergency cesarean sections.
4. Allergy/intolerance to local anesthetic or steroids.
5. Pre-existing neurological and/or anatomical deficit that would preclude regional block.
6. Coexisting coagulopathy such as hemophilia or von Willebrand Disease.
7. BMI > 40.
8. History of intravenous drug or opioid abuse.
9. History of opioid use within a week prior to cesarean section.
10. History of any chronic pain syndrome.

7.0 RANDOMIZATION/RECRUITMENT PROCEDURES

Recruitment: Participants will be recruited, identified, and interviewed by either the study Principal Investigator or one of the co-investigators. The interviewing investigator will confirm eligibility and the absence of any exclusionary criteria. Details of the study (including risks) will be explained to prospective participants to their satisfaction and consent forms will then be signed.

Randomization: Upon enrollment into the study, participants will be randomized to three groups all which will bilateral TAP blocks but the addition of either 2 mg (Group 1) or 4 mg (Group 2) or 0 mg (Control Group) of dexamethasone to the ropivacaine used to perform the TAP block. Randomization will be performed using a random number generator.

8.0 STUDY INTERVENTIONS/PROCEDURES

Study design.

This study is a prospective study, placebo-controlled, double-blinded investigation of the effect of adjuvant dexamethasone in bilateral transverse abdominal plane blocks to prolong the abdominal fascial plane block. Patients undergoing C-section will be screened pre-operatively for inclusion/exclusion criteria. These patients will receive as the standard-of-care neuraxial anesthesia in the form of a spinal anesthetic with bupivacaine for intra-operative pain control, as well as given 0.1mg of intrathecal morphine for post-operative pain control. The patients will then be treated with bilateral

post-operative TAP blocks. This will be a 3-armed study, with each arm receiving the same dose of local anesthetic, 20mL 0.5% ropivacaine, and a different dose of dexamethasone in the block. The patients will receive 0mg (Control Group), 2mg (Group 1), or 4mg (Group 2) of dexamethasone total in bilateral blocks by the anesthesia team in the OR. The dose of dexamethasone will be split between the two sides of the block. Post-operative use of pain medication, pain scores, time until first opioid dose, and opioid requirement in the first 24 hours by the PACU and floor nurses, and these will be recorded in the electronic medical record. Satisfaction scores and estimation of TAP block duration will be assessed and recorded by anesthesia personnel approximately 24 hours post-operatively.

Comparison groups.
The Control Group, as noted above, will also receive spinal anesthetic with bupivacaine and intrathecal morphine and then post-operative bilateral TAP blocks. The same post-operative measures will be obtained from this group as from the Groups 1&2.

Study and timeline of interventions.

Preoperatively: informed consent will be obtained by a member of this study. The patients will be screened for inclusion/exclusion criteria on day of procedure, and then they will be randomized to one of three groups.

Intraoperatively: The anesthesia team involved with care of patient in the operating room will provide routine anesthesia care during the cesarean section including neuraxial anesthesia with intrathecal bupivacaine and morphine.

After completion of the procedure, the patients will receive bilateral TAP block procedure while still in OR. All blocks will include 20mL of 0.5% ropivacaine, and the patients will be randomly assigned a specific dose of dexamethasone at 0mg (given normal saline as control), 2mg, or 4mg respectively. The resident or attending physician supervising the block will be investigators in the study, and they along with the residents performing the blocks will be blinded to the amount of dexamethasone in the injectate.

Postoperatively: The patients will then be monitored in the PACU for approximately 30-60 minutes and then subsequently monitored on an inpatient floor. Pain scores, time until first opioid dose, total opioid requirement will be assessed and recorded. In PACU, these will be recorded every 15-30 minutes. On the inpatient floor, these will be recorded every 6 hours. Satisfaction scores and estimation of TAP block duration will be assessed and recorded by anesthesia personnel approximately 24 hours post-operatively.

Measured Endpoints: VAS scores every 15-30 minutes while in PACU then recorded every 6 hours on the floor for 48 hours; time until first does of opioid, opioid requirement in first 48 hours, subjective patient satisfaction, and estimation of block duration.

Projected Overall Study Timeline

Aug 2015 - Feb 2016	Mar 2016 – Dec 2016	Jan 2017 – Feb 2017	Mar 2017
Study Start-Up			
	Enrollment		
		Data Entry and Analysis	
			Study Write-Up

9.0 STATISTICAL CONSIDERATIONS

Demographic Variables: Patient age, BMI, co-morbidities.

Control Variables: Dexamethasone dose (0 mg, 2 mg, or 4 mg).

Primary Study Variables: The primary endpoint for this study is the duration of TAP block. This endpoint will be assessed within 48 hours post-surgery.

General Data Analysis: All demographic and clinical variables with continuous measures will be expressed as means and standard deviations; categorical factors will be expressed as proportions. For non-normal data, the medians and inter quartile ranges will be displayed. The distribution of the continuous factors will be examined using the Kolmogorov-Smirnov test. For data that are normally distributed, one-way ANOVA will be used to compare groups of data. For data that are not normally distributed, the Kruskal-Wallis test will be used for comparisons. Chi-square and Fisher's exact tests will be used to analyze categorical data. For all comparisons, a value of $p < 0.05$ will be considered statistically significant.

Primary Outcome Analysis: Statistical analyses will be performed using SAS for Windows, version 9.2. One-way ANOVA (or the Kruskal-Wallis test, as appropriate) will be used to compare duration of TAP block for the three groups. Linear regression will also be used to test the relationship between duration of block and dexamethasone dose, while controlling for relevant clinical and demographic variables.

Secondary Outcome Analysis: One-way ANOVA (or the Kruskal-Wallis test) will be used to compare the groups on post-operative pain scores, opioid requirements, and patient satisfaction scores.

Additional Data Analysis: N/A

Statistical Power and Sample Size Estimates: Approximately 69 subjects (23 per group) are expected to be enrolled in this study. Given this sample size and assuming that the average duration of TAP block is 18 hours for the control group, 22 hours for the 2 mg of dexamethasone group, and 24 hours for the 4 mg of dexamethasone group, this study will have approximately 80.9% power to detect a difference in block duration, assuming a common standard deviation of 6 hours. If the variability in block time is smaller than 6 hours, this study will have greater power.

10.0 PATIENT SAFETY AND DATA SECURITY MONITORING

Assessment of Level of Risk: Minimal Risk
Participants in this study have the risk associated with a TAP block including pain and discomfort from the procedure, excessive bleeding, infection, nerve damage, failed analgesia, and allergic reaction to local anesthetic. Also, given the location of the block, the patient does have a risk for intraperitoneal injection.

Oversight of this investigation will be provided by:
Oversight for this clinical study will be provided by principal investigator (PI), Joel Feinstein M.D., who is an Assistant Professor in Anesthesiology (attending) at the University of Alabama at Birmingham (UAB). The study's primary co-investigator, Timothy Torres M.D., who is a resident in Anesthesiology at UAB.

The mechanisms for HIPAA compliance [including a detailed electronic personal health information (PHI) data path]:

The patient's name, medical number and date of surgery will be entered onto a list maintained on the Department of Anesthesiology's Clinical Research Server and associated with a unique patient study ID number. Notably, the Clinical Research Server is HIPAA compliant, has researcher specific restricted access, and is password protected. This research server is backed up to another secure research server at a different location..

All data that is gathered will be associated with the patient's study ID number which will be listed on all study documents. Study data will be entered onto standardized, preprinted data collection sheets. The study data will be collected, scanned and stored on the Department of Anesthesiology's Clinical Research Server. The original paper data collection forms will be disposed of using the UAB contracted confidential shredding service after the de-identified data have been transferred to the password-protected, computer database.

A data and safety monitoring plan will be implemented by Drs. Feinstein and Torres to ensure that there are no changes in the risk/benefit ratio during the course of the study and that confidentiality of research data is maintained. Investigators and study personnel will meet either electronically or in person, monthly (more often if needed) during active participant enrollment to discuss the study (e.g., study goals and modifications of those goals; subject recruitment and completion; progress in data coding and analysis; documentation, identification of adverse events or research subject complaints; violations of confidentiality) and address any issues or concerns at that time, including delaying surgery for the testing. The Department of Anesthesiology's Human Studies Research Committee will serve as the Data Safety Monitoring Board for this study and will review the project quarterly.

All personnel who are involved in the design or conduct of this research study will have successfully completed required IRB training which includes the importance of measures to protect patient confidentiality.

11.0 REPORTING ADVERSE EVENTS

For the purposes of this study, serious adverse events will be noted in the course of routine intraoperative and postoperative care and addressed at that time. They will be reported to existing departmental and institutional programs.

Specifically, any adverse events occurring in these study participant patients will be reported immediately to the UAB Department of Anesthesiology Human Subjects Research Committee and the UAB IRB. As an integral element of data and patient safety monitoring, a completed departmental-level Data Protection and Patient Safety Monitoring Form will be presented to the UAB Department of Anesthesiology Human Subjects Research Committee every three months.

12.0 REFERENCES CITED (minimum of 10 citations)

1. Baeriswyl M, Kirkham KR, Kern C, Albrecht E. The Analgesic Efficacy of Ultrasound-Guided Transversus Abdominis Plane Block in Adult Patients: A Meta-Analysis. Anesth Analg. 2015 Sep 22;PubMed PMID: 26397443.

2. Srivastava U, Verma S, Singh TK, Gupta A, Saxsena A, et al. Efficacy of trans abdominis plane block for post cesarean delivery analgesia: A double-blind, randomized trial. Saudi J Anaesth. 2015 Jul-Sep;9(3):298-302. PubMed PMID: 26240550; PubMed Central PMCID: PMC4478824.

3. Aydogmus M, Sinikoglu S, Naki M, Ocak N, Sanlı N, et al. Comparison of analgesic efficiency between wound site infiltration and ultra-sound-guided transversus abdominis plane block after cesarean delivery under spinal anaesthesia. Hippokratia. 2014 Jan;18(1):28-31. PubMed PMID: 25125948; PubMed Central PMCID: PMC4103037.

4. Kanazi GE, Aouad MT, Abdallah FW, Khatib MI, Adham AM, et al. The analgesic efficacy of subarachnoid morphine in comparison with ultrasound-guided transversus abdominis plane block after cesarean delivery: a randomized controlled trial. Anesth Analg. 2010 Aug;111(2):475-81. PubMed PMID: 20488929.

5. McDonnell JG, Curley G, Carney J, Benton A, Costello J, et al. The analgesic efficacy of transversus abdominis plane block after cesarean delivery: a randomized controlled trial. Anesth Analg. 2008 Jan;106(1):186-91, table of contents. PubMed PMID: 18165577.

6. Shahraki AD, Feizi A, Jabalameli M, Nouri S. The effect of intravenous Dexamethasone on post-cesarean section pain and vital signs: A double-blind randomized clinical trial. J Res Pharm Pract. 2013 Jul;2(3):99-104. PubMed PMID: 24991614; PubMed Central PMCID: PMC4076920.

7. Akkaya A, Yildiz I, Tekelioglu UY, Demirhan A, Bayir H, et al. Dexamethasone added to levobupivacaine in ultrasound-guided tranversus abdominis plain block increased the duration of postoperative analgesia after caesarean section: a randomized, double blind, controlled trial. Eur Rev Med Pharmacol Sci. 2014;18(5):717-22. PubMed PMID: 24668714.

8. Ammar AS, Mahmoud KM. Effect of adding dexamethasone to bupivacaine on transversus abdominis plane block for abdominal hysterectomy: A prospective randomized controlled trial. Saudi J Anaesth. 2012 Jul;6(3):229-33. PubMed PMID: 23162395; PubMed Central PMCID: PMC3498660.

9. Liu J, Richman KA, Grodofsky SR, Huffman GR, Kelly JD, Glaser DL, Elkassabany N. Is there a dose response of dexamethasone as adjuvant for supraclavicular brachial plexus nerve block? A prospective randomized double-blinded clinical study. Journal of Clinical Anesthesia. 2015 Jan; 27(3): 237-242.

10. Hutchinson S, Marmura MJ, Calhoun A, Lucas S, Silberstein S, et al. Use of common migraine treatments in breast-feeding women: a summary of recommendations. Headache. 2013 Apr;53(4):614-27. PubMed PMID: 23465038; NIHMSID: NIHMS566022; PubMed Central PMCID: PMC3974500.

11. Janssen MN, Genta MS, et al. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. Journal of AMA. 2000 Mar; 160(5):610-619.

APPENDIX A (Starting as a new page) (For Internal Departmental Use **Only**)

STUDY BUDGET AND FUNDING SOURCES

Study Title: Dose Escalation of Dexamethasone to Increase Duration of Transversus Abdominal Plane Block Following Cesarean Section. A Prospective Randomized Double-Blinded Clinical Study.

Principal Investigator: Joel Feinstein, M.D.

Itemized Budget:

Is extramural funding presently being sought for this study? No
If yes, from what source or agency? N/A
If not now, is this planned at some point in the future? No
Please provide brief pertinent details: The purchase of the medication for this study, ropivacaine and dexamethasone, will be paid for through departmental funds. We will request support through CAAP and RMRET mechanisms.