STUDY PROTOCOL

Transversus Abdominis Plane Blocks with and without Dexamethasone: A Randomized Clinical Trial in Minimally Invasive Colorectal Surgery

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PROTOCOL

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Title: **Transversus Abdominis Plane Blocks with and wthout Dexamethasone: A Randomized Clinical Trial in Minimally Invasive Colorectal Surgery**

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Additional Canadian trial sites may be added in future.

Background Information

Minimally invasive colorectal surgery has dramatically improved postoperative outcomes, resulting in significantly shorter length of stay, pain, and overall cost. [1] Despite the advances in multimodal analgesia and enhanced-recovery pathways, the optimal strategy for perioperative analgesia has not yet been defined, and there may be a role for expanded use of regional anesthesia in minimally invasive surgery.

Regional anesthesia, specifically the transversus abdominis plane (TAP) block, has been shown to reduce postoperative pain and opioid requirements even in the context of minimally invasive surgery. [2,3,4,5,6] Surgeon-performed, laparoscopically placed TAP blocks are equivalent, or perhaps superior, to ultrasound-guided TAP blocks[7,8]. Long-acting local anesthetics, specifically liposomal bupivacaine, have been shown to prolong the effect of TAP blocks over non-liposomal bupivacaine[910], and has also suggested a reduced length of stay and less overall cost, despite the high cost of the formulation.[11] These findings suggest improved outcomes can be expected if a longer block can be achieved.

Liposomal bupivacaine is not currently available in Canada and is very costly. In addition, recent evidence has called into question the efficacy of liposomal bupivacaine, specifically regarding rebound pain. Rebound pain can occur with any type of regional anesthesia, but intravenous corticosteroids seem to mitigate this problem.[12]

We hypothesize that addition of dexamethasone to bupivacaine can prolong the duration of sensory block to be similar to that achieved with liposomal bupivacaine, but at a much lower cost. Dexamethasone was chosen due to its current widespread use in regional anesthesia, long biological half-life (36-54 hours), low cost, availability, and absence of any evidence of harm with single-dose use.

Regional anesthetic supplemented with perineural dexamethasone, a potent corticosteroid, has shown improved efficacy and prolonged duration of anesthetic in a variety of regional anesthetic techniques as well as in spinal anesthesia.[13,14 ,15] The duration of sensory block can be nearly doubled when dexamethasone is combined with long-acting local anesthetics for perineural anesthesia in brachial plexus and interscalene blocks. [1617]

Dexamethasone in combination with local anesthetic has been the subject of several meta-analyses and systemic reviews, which universally suggest a synergistic effect on duration of sensory block. [181920]. It remains unclear whether the effect is greater with systemic or perineural administration, with moderate quality evidence suggesting a stronger effect from perineural administration.[21]

The adjunctive analgesic effect of dexamethasone is thought to be mediated by attenuating the release of inflammatory mediators, reducing ectopic neuronal discharge, and inhibiting potassium channel-mediated discharge of nociceptive C-fibres. Corticosteroids possess potent anti-inflammatory effects. Dexamethasone as an adjunct to local anesthetic is thought to work through reduction in inflammatory mediators, less ectopic neuronal discharge, and reduced potassium channel-mediated transmission in nociceptive C-fibres[222324]. Local vasoconstriction may also play a role.[25] However, the exact mechanism by which dexamethasone reduces pain remains unknown. It also remains unclear whether the proven analgesic benefits are due to local (perineural) or systemic effects. While controversial, the burden of evidence points to increased effect from perineural administration. [26]

Local (incisional) subcutaneous injection of dexamethasone may also provide analgesic benefit. In a placebo-controlled randomized trial assessing subcutaneous injection of 16mg dexamethasone into cesearean-section incisions against intravenous administration of the same dose and a placebo group, local injection was found to have significantly less postoperative pain than the other two groups. In addition, the local injection group had less postoperative nausea than the placebo group, suggesting a protective effect against postoperative nausea and vomiting.[27]

There are no known safety concerns about single-dose perioperative dexamethasone, and no reports of harm could be identified with its use as an adjunct to regional anesthesia. Three studies have reported on potential harms with administration for brachial plexus block; no prolonged nerve palsies were identified in 407 patients.[28][29][30] One study reported a minor, but clinically insignificant, rise in blood glucose concentration. A 2018 Cochrane review examined adverse side effects of dexamethasone in surgical patients and concluded that there was no effect on surgical site infection, unclear effects on wound healing, and a transient (<12 hour) mild rise in blood glucose concentration of uncertain significance. The effect was similar for low (4-5mg), moderate (8-10mg) or high (12-20mg) doses[31]. Notably, this review assessed effects of intravenous dexamethasone, which would be expected to have more pronounced systemic effect than perineural injection.

Although widely used in clinical practice, adjunctive application for regional anesthesia is an off-label use. Dexamethasone has not been approved for perineural administration by Health Canada, the United States Food and Drug Administration, nor any other regulatory body.

Trial Objectives and Purpose

The objective of this trial is to investigate the effect of adjuvant dexamethasone in combination with bupivacaine to increase the depth and duration of sensory block in laparoscopically placed transversus-abdominis plane (TAP) blocks. The primary outcome will be total opioid consumption, in hydromorphone equivalents, in the first 48 hours after surgery. Secondary outcomes will be length of stay in the post-anesthetic care unit (PACU) and length of stay in hospital. The results of this study will serve as a proof-of-concept and will guide future research exploring adjuvant dexamethasone use in TAP blocks, specifically optimal dosing and ultimately a head-to-head comparison with systemic dexamethasone.

The results of this study will be of benefit to patients presenting for colorectal surgery, and more likely any type of abdominal surgery. Further research and refinement of regional anesthesia protocols adds to the armamentarium of anesthetic modalities available to anesthesiologists and surgeons and may offer a strategy for improved patient care.

Trial Design

This study will be carried out as a prospective, randomized, single-blinded clinical trial.

The intervention group will receive intraoperative laparoscopically assisted, surgeon-placed TAP blocks using 1mL/kg of 0.25% bupivacaine with epinephrine 1:200,000 combined with 16mg dexamethasone divided into 4 aliquots to be placed at two locations per side along the anterior axillary line between the

costal margin and the iliac crest. The control group will have TAP blocks with the same dose of bupivacaine without dexamethasone. The blocks will be performed at the conclusion of surgery. Postoperatively, all patients will be provided with patient-controlled analgesia (PCA) with institutional standardized orders.

Intravenous dexamethasone will not be given for prevention of postoperative nausea and vomiting (PONV); prophylaxis of postoperative nausea and vomiting will be at the discretion of the anesthesiologist, but can include any of ondansetron, haloperidol, or dimenhydrinate. If PONV occurs and is refractory to non-corticosteroid treatment, dexamethasone may be given for treatment but would result in exclusion from the trial. General anesthetic technique will be at the discretion of the anesthesiologist, but the following adjunct anesthetic drugs will not be permitted, due to independent effects on postoperative pain: dexmedetomidine, lidocaine, and ketamine.[323334] These adjuncts are occasionally used in anesthetic protocols, but their exclusion will not affect the quality of the anesthetic provided, and their use is not considered standard of care. All patients will be provided with a standardized hydromorphone-based patient-controlled analgesia (PCA) for a minimum of 48 hours postoperatively.

The primary outcome will be total opioid consumption, in hydromorphone equivalents, in the first 48 hours after surgery. Secondary outcomes will be length of stay in the post-anesthetic care unit (PACU), length of stay in hospital, and total opioids administered in the PACU.

A computer-generated random number table will be used to randomize patients to receive either bupivacaine alone (n=60) or bupivacaine plus dexamethasone (n=60). Allocation will be performed in a 1:1 ratio. Group allocation will be concealed via a centralized third-party research assistant. Group allocation will be blinded to study participants, study investigators, post-anesthetic care unit (PACU) nursing staff, and surgical ward nursing staff. The attending surgeon and attending anesthesiologist on the day of surgery will not be blinded to the intervention, however, they will be asked to conceal the anesthetic modality from the PACU staff and ward nurses. The intervention will be charted in the Operating Room record, but not on the anesthetic record. PACU nurses commonly review the anesthetic record, whereby they would discover the intervention.

A blinded, centralized, third-party research assistant or study investigators will carry out data collection. Postoperative opioid consumption will be quantified through chart review as well as assessment of patient-controlled analgesia (PCA) usage at 24 and 48 hours following the operation. Recording the doses of opioids administered in the medication administration record (MAR) is standard practice by PACU nursing staff at the study institution. PCA pumps automatically document cumulative opioids administered and can easily be checked at the bedside, as well as being recorded in the MAR. Length of stay in hospital is readily available from the chart.

Followup for primary and secondary outcomes will be limited to 48 hours postoperatively, and assessment of infiltration sites for complications will be performed at 6 weeks postoperatively.

Stopping Criteria

Interim analysis will be performed after 50% enrolment. If either arm is found to be superior, the trial will be discontinued. If any adverse events are identified in either arm, a safety review will be performed. Should a significant safety concern be identified, the trial will be discontinued.

Pharmacokinetics and Pharmacodynamics– Bupivicaine[35]

Pharmacodynamics and Pharmacokinetics
Onset of action: Anesthesia (route and dose dependent):
Epidural: Up to 17 minutes to spread to T6 dermatome (Scott 1980).
Infiltration: Fast (Barash 2009); Dental injection: 2 to 10 minutes.
Spinal: Within 1 minute; maximum dermatome level achieved within 15 minutes in most cases.
Duration (route and dose dependent):
Infiltration: 2 to 8 hours (Barash 2009); Dental injection: Up to 7 hours.
Distribution: V_d: Infants: 3.9 ± 2 L/kg; Children: 2.7 ± 0.2 L/kg.
Protein binding: 84% to 95%.
Metabolism: Hepatic; forms metabolite (pipecoloxylidine [PPX]).
Half-life elimination (age dependent): Implant: 19 hours; Injection: Neonates: 8.1 hours; Adults: 2.7 hours; Subacromial injection: 16.4 to 26.1 hours.
Time to peak, plasma: Caudal, epidural, or peripheral nerve block: 30 to 45 minutes; Implant: Median: 3 hours (range: 1.5 to 24 hours); Subacromial injection: Median: ~6 to 8 hours (range: 1 to ~27 hours).
Excretion: Urine (~6% unchanged).
Clearance: Infants: 7.1 ± 3.2 mL/kg/minute; Children: 10 ± 0.7 mL/kg/minute.

Pharmacokinetics and Pharmacodynamics– Dexamethasone[36]

Onset of action: IV: Rapid.
Immune thrombocytopenia: Oral: Initial response: 2 to 14 days; Peak response: 4 to 28 days (Neunert 2011).
Duration: IV: Short.
Absorption: Oral: 61% to 86% (Czock 2005).
Metabolism: Hepatic.
Half-life elimination:
Adults: Oral: 4 ± 0.9 hours (Czock 2005); IV: ~1 to 5 hours (Hochhaus 2001; Miyabo 1981; Rohdewald 1987; Tóth 1999).
Time to peak, serum: Oral: 1 to 2 hours (Czock 2005); IM: ~30 to 120 minutes (Egerman 1997; Hochhaus 2001); IV: 5 to 10 minutes (free dexamethasone) (Miyabo 1981; Rohdewald 1987).
Excretion: Urine (~10%) (Duggan 1975; Miyabo 1981).

Selection and withdrawal of subjects

We intend to enroll a sample size of 120 patients based on an alpha set at 0.05, power set at 0.08, and the effect size set at 0.8.

Inclusion criteria are: age > 18, ASA class I-III patients scheduled for elective or urgent inpatient laparoscopic/laparoscopic assisted colorectal surgery.

Exclusion criteria are: emergency surgery, open surgery, contraindications to laparoscopic surgery (ie. adhesions, inability to tolerate pneumoperitoneum), ASA class ≥ 4, age < 18, pregnant or breastfeeding women, significant cardiorespiratory/hepatic/renal disease, allergy to any study drugs, inability to consent, inability to respond to pain assessments, inability to use the patient-controlled analgesia device (PCA), preoperative chronic opioid use.

Potential participants will be identified by their attending surgeon during their initial clinic surgical consultation. This typically occurs several weeks in advance of their scheduled surgical procedure. Information detailing the study, as well as contact information of the research team will be made available to patients at this time should they have any questions. After having had a chance to review the study information provided to them by their surgeon, prospective patients will be assessed by study staff (attending surgeon or designate such as a general surgery resident) and asked to sign a consent if they agree to participate and meet the inclusion criteria. The consent will be taken on the day of surgery.

Participants who are unable to personally provide informed consent will be excluded from the study. No third party will be allowed to consent on the participants behalf. Capacity will be assessed by the study staff or designate obtaining consent. All patients participating must be assessed to determine that they fully understand the protocol, risks, and benefits of participating in the study.

Subjects will be free to withdraw voluntarily from the study at any point. The process for withdrawal can be initiated by the participant at any time by informing any of the study staff of the decision to withdraw. No explanation for withdrawal will be sought. If this occurs prior to randomization, no patient information will be collected for study purposes, and the patient will still be eligible to undergo surgery as planned without compromise to care. If withdrawal occurs during data collection, data collected on the subject will be destroyed, and they will continue receiving post-operative care as per standards. Either of the attending anesthesiologist or attending surgeon caring for the patient on the day of surgery has the ultimate discretion as to whether a patient is included or excluded from the study. If the attending surgeon or anesthesiologist deems the patient unfit to participate in the study, this will be communicated to the study coordinator, and the patient will be withdrawn. All adverse events and protocol deviations will be reported to the study coordinator, study investigators, and appropriate Research Ethics Board. Subjects who are withdrawn from the study due to the occurrence of an adverse event will be followed up by one of the study's physician investigators while in hospital. If the adverse event is believed to have been related to the study drug, a detailed note will be made in the patient's medical record and passed on to future care providers. Subjects withdrawn from the study due to an adverse event will not be replaced. Any adverse events will result in unblinding by notification of the principle investigator.

Treatment of subjects

All study subjects will be assessed by an anesthesiologist in the Preoperative Assessment Clinic (PAC) prior to their scheduled procedure date. At this time, subjects will undergo a comprehensive medical assessment, including a review of their current prescription medications. At the discretion of the reviewing

anesthesiologist, subjects will be counselled regarding which medications may be safely continued or held prior to their procedure.

All subjects will receive standard anesthetic, analgesic, amnestic, and anxiolytic medications under the care of a qualified anesthesiologist. Vasopressors will be used when appropriate as part of standard practice in the operating room. The choice of anesthetic technique will be at the discretion of the treating anesthesiologist, however the anesthetic adjuncts of dexmedetomidine, lidocaine, and ketamine will not be permitted due to significant potential for confounding due to independent effect on postoperative pain.

All patients will be premedicated with acetaminophen 975 mg on the day of their scheduled procedure in the Same Day Surgery (SDS) unit prior to arriving in the operating room. Once in the operating room, standard monitors including noninvasive blood pressure, electrocardiography, pulse oximetry, and capnography will be applied as per Canadian Anesthesiologists' Society (CAS) guidelines. Neither group will receive systemic dexamethasone for PONV prophylaxis; alternative PONV prophylaxis may include ondansetron or haloperidol, to be given at the discretion of the treating anesthesiologist.

Both groups will receive surgeon-placed, laparoscopically visualized transversus abdominus plane (TAP) block at the end of the surgical procedure prior to emergence from anesthesia as an analgesic adjunct using 1mL/kg of 0.25% bupivacaine with epinephrine 1:200,000 divided in four aliquots to be placed at two locations per side along the anterior axillary line between the costal margin and the iliac crest. The intervention group will have dexamethasone 16mg combined with the bupivacaine / epinephrine, with 4mg to be injected at each TAP site, for a total of 8mg dexamethasone per side. The study drug will be provided from wardstock available in the operating room, and will be prepared by nursing staff as per standard perioperative nursing practice. The control group will have TAP blocks with the same dose of bupivacaine without dexamethasone. The bupivacaine / lidocaine solution will be sourced from the hospital pharmacy, and is purchased from Sandoz Canada

Currently, the colorectal surgeons based at Royal University Hospital are experienced with performance of TAP blocks and have been performing them for several years. If there is interest from other general surgeons in participating in the trial, in-person training will be provided to that surgeon by one of the experience surgeons to ensure standardization of the technique.

Following surgery, patients will be extubated fully awake in the operating room and transferred to the PACU. In PACU, both groups will have access to nurse-administered multimodal analgesia including rescue hydromorphone for postoperative pain relief. Standard antiemetics will be available as well. Upon discharge from PACU, hydromorphone-based patient-controlled analgesia (PCA) will be initiated and continued for a minimum of 48 hours postoperatively. Morphine-based PCA can be substituted if there is a contraindication to hydromorphone. Both groups will receive acetaminophen 975mg PO Q6H scheduled for 48 hours then PRN.

Surgical ward nurses will be not informed that the patient is involved in the study, as participation is not relevant to postoperative care, which will be administered as per usual. The study institution maintains a standardized colorectal-surgery postoperative pathway directing advancement of diet, intravenous maintenance fluids, deep-vein thrombosis prophylaxis, and urinary catheter management.

Assessment of efficacy

The primary efficacy outcome of this study will be total opioid consumption, in hydromorphone equivalents, at 24 and 48 hours postoperatively. Secondary outcomes will be length of stay in the post-anesthetic care unit (PACU), length of stay in hospital, and total opioids administered in the PACU.

Assessment of safety

Following surgery, adequacy of analgesia will be closely monitored, and inadequate analgesia will be treated as per standard protocol in the postanesthetic care unit (PACU). Physical examination of the TAP block injection sites will be performed daily and at the 6 week postoperative follow up visit. Diabetic patients will have blood glucose monitoring as per standard protocol, and all patients will have serial vital signs four times daily. Clinical assessment for severe postoperative nausea and vomiting (PONV) will be performed as per nursing protocol, and by the attending anesthesiologist on daily round. Any serious adverse events will be followed closely until resolution, with frequency of follow up to be determined by clinical judgement. Education to ward nurses will be provided on identification and reporting of adverse events. Adverse events will be recorded in the data collection tool. All serious adverse events will be reported to the Research Ethics Board and Health Canada as per the University of Saskatchewan Serious Adverse Events Reporting Policy and the Health Canada Guidance for Clinical Trial Sponsors document. Any serious unexpected adverse drug events will be reported to Health Canada. During the course of the trial, the sponsor will inform Health Canada of any serious unexpected adverse drug reaction (SUARD) as follows:

- (a) if it is neither fatal nor life threatening, within 15 days after becoming aware of the information; and
- (b) if it is fatal or life threatening, within seven days after becoming aware of the information.

Definitions of reactions are as follows:

Serious Adverse Drug Reaction: An adverse drug reaction that requires in-patient hospitalization or prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening or that results in death.

Serious Unexpected Adverse Drug Reaction (SUADR): A serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out in the investigator's brochure or on the label of the drug.

Statistics

Primary Outcome:

Total opioid consumption at 24 and 48 hours will be gathered from the PCA record and Medication Administration Record (MAR). Intention to treat analysis will be performed. Parametric data will be analyzed with the students t-test for statistical significance.

Secondary Outcome: Opioid consumption in the PACU will be reported in hydromorphone equivalents and compared with chi square test. Length of stay in PACU and length of stay in hospital will be reported as a mean +/- standard deviation (SD), along with confidence intervals and compared with chi square test.

Interim Analysis

Interim analysis for primary and secondary outcomes, as well as safety parameters, will be performed upon completion of 50% of the total recruitment. If statistically significant superiority of either arm is identified, the trial will be terminated.

Direct access to source data / documents

The Investigator acknowledges that some authorities have a duty to monitor the study records to make sure all the information is correct. The study records may be inspected in the presence of the investigator or his qualified designate by representatives of Health Canada or the University of Saskatchewan Biomedical Research Ethics Board for quality assurance and/or regulatory purposes.

Quality Control and Quality Assurance Procedures

Patients will be monitored intraoperatively by a qualified staff anesthesiologist. Following surgery, patients will be extubated fully awake in the operating room and transferred to the PACU with supplemental oxygen. In PACU patients will be monitored by dedicated nursing staff and will have access to nurse-administered analgesia. Standard antiemetics will be available as well, and dexamethasone can be given systemically as a rescue antiemetic. If this occurs, the patient will be excluded from the study. Following discharge from PACU, patients will be monitored on the ward by nursing staff and postoperative care will be administered as per usual protocol.

Ethics

The Investigator will ensure that this study is conducted in full compliance with the principles of the Declaration of Helsinki and with the laws and regulations in Canada. This clinical study will be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice.

This study (including protocol and proposed consent form) has been submitted to the University of Saskatchewan Biomedical Research Ethics Board. Eligible subjects will only be included in the study after providing written BREB-approved consent.

Data handling and record keeping

All information collected on the data collection form will be de-identified and no direct personal identifiers will be recorded. All measures will be taken to maintain confidentiality on collected data; however, there is a chance of unintentional release of information connecting the subject with the study. A list connecting

the subject's name to the subject study number listed on the data collection form will be stored in a password-protected computed kept in the locked office of the principal investigator, located at Royal University Hospital, Saskatoon. Access to this list will be limited to study staff, and it will be destroyed upon study completion through the confidential paper shredding services of the Royal University Hospital.

Data will be stored for 25 years, as per the Health Canada requirements. The Investigator is responsible to archive the documents/data for the required period of time.

Financing

This study has received funding of $10,000 from the Department of Surgery, University of Saskatchewan.

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