Title: Analgesic Efficacy of Surgeon-administered Transversus Abdominis Plane Blocks for Caesarean Section

Short title: Analgesic efficacy of surgeon-administered TAP block for CS

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1. The Need for a Trial

1.1 What is the problem to be addressed?

Caesarean section (CS) is currently the most commonly performed major surgery in the world (1), with the global rate increasing progressively from around 7% in 1990 to 21.1% today (2). In Canada, the rate has risen from 18.7% in 1997 to 31.0% in 2020 (3). Accompanying this trend is the issue of postoperative pain, which poses a significant challenge to postpartum recovery and is recognized as a significant public health issue. In patients undergoing CS, one in five report severe acute pain after the procedure (4). Inadequate postoperative analgesia is associated with delayed ambulation, prolonged hospital stay, increased opioid consumption, and increased postpartum depression (5).

Amidst the ongoing opioid crisis, the risk of narcotic over-prescription, dependence, and addiction is especially salient. One study found that 1 in 300 women develop opioid use disorder after CS (6). Efforts to distribute narcotics judiciously must be balanced with adequate postoperative analgesia, as studies have also shown that poorly controlled postoperative pain is associated with chronic pain after CS (7). Current guidelines on enhanced recovery after surgery (ERAS) emphasise the use of multimodal postoperative analgesic regimens to decrease opioid reliance and improve recovery after CS (8).

Post-CS ultrasound (US)-guided transversus abdominis plane (TAP) block has been included as part of a multimodal analgesic regime with established and effective postoperative analgesic properties (9), (10). Its use has the potential to decrease postoperative pain (11) with a reduced side effect profile compared to other regional blocks (12). However, a simpler and faster approach to conventional US-guided TAP block is an intraoperative TAP block performed by the surgeon at the time of CS (13). The transperitoneal technique is described by Owen et al (13), whereby after uterine closure, the rectus muscles are retracted outwards and under direct visualization, local anaesthetic is infiltrated into the transverse abdominis plane through the parietal peritoneum by the surgeon. Despite the theoretical benefits of enhanced analgesic effect and shorter procedure time compared to the US-guided alternative (11), (13), there is limited data on the effectiveness of surgeon-administered TAP (S-TAP) blocks for patients undergoing CS.

1.2 What is/are the principal research question(s) to be addressed?

Does the use of S-TAP blocks reduce postoperative pain in patients undergoing elective CS?

1.3 Why is a trial needed now? E.g. Provide evidence from the literature. Furthermore, give references to any relevant systematic review(s)1 and discuss the need for your trial in the light of the(se) review(s). If you believe that no relevant previous trials have been done, give details of your search strategy for existing trials.

While there is robust literature attesting the efficacy of intrathecal morphine in post-operative analgesia following CS under spinal anesthetic, using additional modalities for pain management is still valuable in further optimizing post-operative recovery and long term pain outcomes (8,9,12,14). This modality may be of particular use when intrathecal morphine is not available (ex: CS under general anesthetic, morphine allergies).

Despite more data available on the use of US-guided TAP blocks (15), limited information exists on the efficacy and feasibility of S-TAP blocks for patients undergoing CS. S-TAP may be a useful alternative when US access is limited, such as in patients with obesity where US visualization is difficult(16), or in low-resource settings where US technology is not accessible (17). The transperitoneal approach would also decrease risk of serious complications associated with US-guided TAP blocks, such as puncture injury or perforation of underlying abdominal organs and vasculature.

We recently performed a systematic review to assess the efficacy of S-TAP blocks and their potential role in multimodal analgesic protocols for postoperative CS patients. While we were only able to identify six studies specifically evaluating S-TAP blocks, the results were promising in favour of S-TAP blocks when compared to control (13,18–22).

Two studies compared S-TAP vs. US-guided TAP and did not show any significant differences in analgesic effect, but did find a significant reduction in time required to perform TAP blocks intraoperatively (19,22). Three of four studies comparing S-TAP to no TAP (or saline placebo) showed S-TAP block provided superior analgesia that was statistically significant across measurements of patient reported pain scores (by VAS) at 24 hours postoperatively, time to first request for rescue analgesia, and total opioid consumption in the first 24 hours postoperatively (13,18,19,21).

Although statistical significance was reported for three of the studies' outcomes, this should be interpreted in the context of a high risk of bias for all studies (13,18,21). Additionally, the identified studies were non-homogenous and all with high risk of bias, rendering it challenging to draw conclusions from. The limitations of the review are largely rooted in the paucity of clinical research around S-TAP blocks. This is especially applicable in the pregnant and postpartum population, often excluded as "drug orphans" in the realm of pharmacologic research (23).

Given that insufficient and non-homogeneous data were available to definitively draw firm conclusions regarding the efficacy of S-TAP blocks, a large randomized clinical trial with adequate power is needed to investigate whether S-TAP blocks have a role in optimizing postoperative analgesia and pain-related outcomes in CS.

In summary, preliminary work on S-TAP blocks versus controls at time of CS shows promise as an effective and feasible means of optimizing analgesia, improving patient satisfaction, and reducing opioid consumption after CS (13,18,20,21). S-TAP blocks appear to be equally effective as US-guided TAP blocks for analgesia but offer a simpler and faster approach. This is especially relevant for certain populations such as obese patients, and in low-resource settings where US-guided blocks are less accessible (16,18,19,22).

1.4 How will the results of this trial be used? (E.g. contribute to knowledge translation, such as improving understanding, informing decision making and treatment guidelines, etc.)

The lack of clinically relevant evidence in this area poses a significant challenge to practitioners, leaving them to rely on clinical judgment as opposed to evidence-based practice to make decisions surrounding postoperative pain management. The results of this trial would contribute to knowledge translation, support practitioners in making evidence-based decisions, and contribute to existing ERAS protocols for CS.

Overall, the analgesic effects of S-TAP blocks appear to be more effective than controls and could potentially have the additional advantage over US-guided TAP blocks due to shorter procedural time. This may be particularly advantageous in low-resource settings where economic and cultural barriers are a potential obstacle to optimal analgesia (17). S-TAP blocks could also be a beneficial addition to post-operative analgesia for obese patients, bypassing limitations of US penetrance while reducing narcotic requirement (16).

1.5 Are there any risks to the safety of participants involved in the trial? Please describe.

There are minimal risks to the safety of participants involved in the trial. The control group would receive the current standard of care (intrathecal morphine with no TAP block), and thus would not be at risk of increased postoperative pain due to the withholding of adequate postoperative analgesia. Risks of S-TAP block include hematoma formation at the site of injection, drug reaction, or transcutaneous puncture (14,24). As with all local anesthetic use, there are rare cases of systemic toxicity (25,26) that can be reduced by lower anesthetic concentrations and optimizing injection techniques (26). While there are less data reported on S-TAP, one could deduce that direct visualization during injection and infiltration would facilitate a lower chance of rare, but more serious risks associated with transcutaneous US-guided TAP blocks, such as liver puncture and bowel injury (26–29).

2. The Proposed Trial

2.1 What is the proposed trial design? E.g. Open-label, double or single blinded, etc.

Prospective, single-blind randomized controlled trial.

2.2 What are the planned trial interventions? Both experimental and control.

Experimental

A S-TAP block performed by the surgeon at the time of CS will be performed using a modified version of the transperitoneal technique described by Owen et al (13). After uterine closure, the anterior abdominal wall on the contralateral side to the surgeon is elevated and retracted laterally by an assistant. The bowel and uterus is retracted using the surgeon's non-dominant hand, with or without a sponge. Under direct visualization, a blunted spinal needle is inserted lateral to the rectus muscle to avoid injury to inferior epigastric blood vessels. The needle is then gently advanced through the transversus abdominis fascia into the TAP plane, identified at loss of resistance, or 'a pop'. After aspiration to confirm no accidental placement of the needle intravascularly, local anaesthetic is infiltrated into the transverse abdominis plane through the parietal peritoneum by the surgeon at a prespecified dose of 0.25% bupivicaine 0.25 mL/kg. This is repeated on the contralateral side, after which closure of the fascia, subcutaneous tissue, and skin is performed. Of note, the rectus muscle and peritoneum were not closed. The anesthesiologist monitored the patient for any signs of local anesthetic toxicity. All Obstetricians and Residents at our site at the time of the study will be trained in this aforementioned standardized protocol for performing S-TAP blocks. One-on-one training with one of two experienced practitioners (SW and GN) involved with the study will be offered to all providers participating in the study. In addition, we will encourage providers to reference a YouTube video created by a team of our local providers showing how to perform S-TAP (https://youtu.be/6CqxpMCgFpY).

Patients with regional blocks including spinal anesthetic or epidural as well as those under general anesthetic will be included. Patients requiring additional intraoperative analgesia or conversion from regional block to general anesthetic will be excluded. At the time of skin closure, all patients will be administered a single dose of ketorolac 20mg IV.

Postoperative pain management would be standardized with Acetaminophen 1,000mg PO q6h and Ibuprofen 400mg PO q6h. Patient pain scores will be assessed prior to each scheduled dose of analgesia (q6h). At patient request, rescue analgesia with Hydromorphone 1-3mg PO q3h PRN could be administered. If required, patients will be able to request additional narcotic pending clinician assessment and additional doses will be recorded.

Control

No S-TAP block is performed. However, patients would receive the same standardized postoperative pain management as described above, and their pain management will be scored in the same fashion as the intervention group

2.3 What are the proposed practical arrangements for allocating participants to trial groups? E.g. Randomization method. If stratification or minimization are to be used, give reasons and factors to be included.

Randomization of the patients will be performed using a web-based program. Allocation concealment will be performed using sequentially sealed opaque envelopes numbered serially, containing 'S-TAP' or 'Control'.

2.4 What are the proposed methods for protecting against sources of bias? E.g. Blinding or masking. If blinding is not possible please explain why and give details of alternative methods proposed, or implications for interpretation of the trial's results.

Web based allocation will prevent selection bias. Randomization will control for known and unknown confounders. Patients will be blind to whether or not they received the TAP block to prevent differential misclassification of outcomes.

A nurse not involved in the study will prepare the S-TAP syringe away from the view of the patient and there will be no verbal communication of S-TAP administration by the operating room team. Thus, the patient will be blinded to the group assignment.

Postoperative pain will be assessed by a blinded assessor and protect against measurement bias.

2.5 What are the planned inclusion/exclusion criteria?

Inclusion Criteria

- ASA status II to III
- All patients undergoing elective CS under regional at any gestational age.
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Exclusion Criteria

- Known drug allergy to local anesthetics
- NSAID use contraindicated post partum
- Chronic pain disorder or chronic narcotic use/dependence
- Planned vertical abdominal incision
- Planned Cesarean Hysterectomy.
- Placenta Previa or suspected Placenta Accreta.

2.6 What is the proposed duration of treatment period?

The treatment period will begin at the time of CS and extend until discharge.

2.7 What is the proposed frequency and duration of follow up?

One follow-up session is planned for one week post-delivery via phone call.

2.8 What are the proposed primary and secondary outcome measures?

Primary Outcomes

The primary outcome will be pain measured by the visual analogue scale at 12 hours post op.

The VAS will be administered every six hours, prior to each dose of scheduled analgesia (acetaminophen/ibuprofen) until discharge. The VAS is a widely used instrument to assess pain intensity on a scale from zero (no pain) to 10 (worst possible pain). Observations from our clinical experience have demonstrated that a unidimensional measure of pain, such as the VAS, does not adequately reflect the multidimensional patient experience of postoperative pain. Bolstering our clinical observations, evidence shows some patients are willing to accept postoperative pain, despite high VAS scores (van Boekel). Thus, we will further quantify the relationship between VAS and patient perception of their pain experience by simultaneously having patients choose from one of three categorical responses, either 'Yes, I am adequately satisfied, this level of pain is acceptable to me, and I am OK to continue with current pain management', No, I am not satisfied, but this level of pain is acceptable to me, and I am OK to continue with current pain management and do not want Hydromorphone PO now' or 'No, I am in distress, this level of pain is not acceptable to me, and I would like Hydromorphone PO now.'

Time to first request for rescue analgesia in hours (time from S-TAP administration to first request for Hydromorphone rescue analgesia).

Secondary Outcomes

- Procedural duration of performing TAP block
- Time to first request for rescue analgesia in hours.
- Total opioid consumption in the first 24h and 48h mark, postoperatively.
- Length of admission in days post-operatively.
- Adverse effects of S-TAP block, including drug reactions, hematoma formation or pain at the injection site.
- Common adverse effects of opioids, including: nausea, vomiting, pruritus, and sedation will be assessed as a dichotomous variable. Rare complications such as respiratory depression will be documented only if they occur.

2.9 How will the outcome measures be measured at follow up?

The follow-up session planned for one week post-delivery via phone call will be to assess whether or not an opioid prescription was filled, the amount of postoperative opioid consumed, and patient satisfaction with postoperative analgesia.

2.10 What is the proposed sample size and what is the justification for the assumptions underlying the power calculations? Include both control and treatment groups, a brief description of the power calculations detailing the outcome measures on which these have been based, and give event rates, means and medians etc. as appropriate.

Based on the effect estimate from Abdullah et al, a sample size of 30 per group will have 80% power to detect a .80 point improvement in VAS scores.

2.11 If applicable, are health service research issues be addressed? Justify inclusion/exclusion of health economics and quality of life measures. If these measures are to be included full details should be given including power calculations.

Not planned for this study.

2.12 What is the planned recruitment rate? How will the recruitment be organized? Over what time period will recruitment take place? What evidence is there that the planned recruitment rate is achievable?

We plan to recruit 80 patients in total so we are confident we will have sufficient power. As there are typically over 50 elective CS per month at FMC we feel that the trial is feasible.

2.13 Are there likely to be any problems with compliance? On what evidence are the compliance figures based?

No, the nature of the intervention makes problems with compliance with treatment very unlikely. Frequent patient contact postpartum will ensure good compliance with measurement of pain.

2.14 What is the likely rate of loss to follow up? On what evidence is the loss to follow-up rate based?

We are uncertain but this is one of the reasons for the pilot.

2.15 How many centers will be involved?

This will be a pilot study at one center.

2.16 What is the proposed type of analyses?

The primary outcome VAS score will be analysed as a continuous outcome. Mean and median VAS and patient satisfaction scores will be compared between the two groups and mean differences will be calculated. Statistical significance will be determined using a t-test after appropriate transformations.

2.17 What is the proposed frequency of analyses?

One analysis. No interim analysis is planned.

2.18 Are there any planned subgroup analyses?

No.

2.19 Has any pilot study been carried out using this design?

No, this is the pilot study.

3. Trial Management

3.1 What are the arrangements for day to day management of the trial? E.g. Randomization, data handling, and who will be responsible for coordination.

OnCore trial support center at Cumming's School of medicine will provide randomization and data collection services.

4. Additional Considerations

Charts will be reviewed for demographic variables including: BMI prior to CS, height, weight, age, parity, number of previous CS, indication for CS, other prior abdominal surgery, total operative time, cannabis use

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