Original Article

Addition of clonidine to bupivacaine in transversus abdominis plane block prolongs postoperative analgesia after cesarean section

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Abstract

Background and Aims: The aim was to compare duration of postoperative analgesia with addition of clonidine to bupivacaine in bilateral transversus abdominis plane (TAP) block after lower segment cesarean section (LSCS).

Material and Methods: One hundred American Society of Anesthesiologists (ASA) grade I and II pregnant patients undergoing LSCS under spinal anesthesia were randomly divided to receive either 20 ml bupivacaine 0.25% (Group B; $n = 50$) or 20 ml bupivacaine+1ug/kg clonidine bilaterally (Group BC; $n = 50$) in TAP block in a double-blind fashion. The total duration of analgesia, patient satisfaction score, total requirement of analgesics in the first 24 h, and the side effects of clonidine such as sedation, dryness of mouth, hypotension, and bradycardia were observed. $P < 0.05$ was taken as significant.

Results: In 99 patients analyzed, TAP block failed in five patients. Duration of analgesia was significantly longer in Group BC (17.8 ± 3.7 h) compared to Group B (7.3 ± 1.2 h; $P < 0.01$). Mean consumption of diclofenac was 150 mg and 65.4 mg in Groups B and BC ($P < 0.01$), respectively. All patients in Group BC were extremely satisfied ($P < 0.01$) while those in Group B were satisfied. Thirteen patients (28%) in Group BC were sedated but arousable ($P = 0.01$) compared to none in Group B. In Group BC, 19 patients complained of dry mouth compared to 13 in Group B ($P = 0.121$). None of the patients experienced hypotension or bradycardia.

Conclusion: Addition of clonidine 1 μg/kg to 20 ml bupivacaine 0.25% in TAP block bilaterally for cesarean section significantly increases the duration of postoperative analgesia, decreases postoperative analgesic requirement, and increases maternal comfort compared to 20 ml of bupivacaine 0.25% alone.

Key words: Bupivacaine, cesarean section, clonidine, transversus abdominis plane block

Introduction

Various trials have demonstrated the efficacy of transversus abdominis plane (TAP) block as a component of multimodal postoperative analgesia after cesarean section[1] and lower abdominal surgery.[2] TAP block is a regional anesthetic technique that blocks the abdominal wall neural afferents (T7-L1) and significantly reduces the pain associated with lower abdominal surgery. Local anesthetic agents are deposited in the neurofascial plane between the internal oblique and transversus abdominis muscle. The block, first described by Rafi in 2001,[3] is a simple and safe technique for analgesia after cesarean section, whether guided by anatomic landmarks or by ultrasound.

Transversus abdominis plane block in cesarean section has been given with local anesthetics like bupivacaine and ropivacaine with a limited duration of action.[4] Additives to local anesthetics like opioids, ketamine and α2 agonists like clonidine and dexmedetomidine have been successfully used in peripheral nerve blocks and field blocks to increase the duration of postoperative analgesia. The present study was planned to investigate whether addition of 1.0 μg/kg clonidine bilaterally to 0.25% bupivacaine in TAP block increases the duration of postoperative analgesia in lower segment cesarean section (LSCS) or not compared to 0.25% bupivacaine alone.

Materials and Methods

After institutional ethical committee approval, this randomized, double-blind controlled trial was conducted in 100 healthy

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parturients (ASA I and II) scheduled to undergo LSCS under spinal anesthesia (SA).The patients were recruited between August 2012 and January 2013. Patients who refused SA, had any contraindication to regional anesthesia, history of drug allergy or chronic pain, a coagulation disorder or infection at the needle insertion site, a body mass index of >30 kg/m^2, or were unable to communicate in either English or Hindi language were excluded from this study. Patients in whom SA was inadequate for the conduct of surgery were also excluded from the study. The study was registered with Clinical Trials Registry of India (www.ctri.nic.in; CTRI/2013/10/004042).

Patients were divided into two equal groups of fifty each to receive either:
Group B (n = 50): TAP block with 20 ml of 0.25% bupivacaine bilaterally.
Group BC (n = 50): TAP block with 20 ml of 0.25% bupivacaine + 1.0 μg/kg clonidine bilaterally (total dose-2.0 μg/kg).

Patients were allocated to the respective groups using a computer-generated random number table. Group allocation was concealed in serially numbered sealed, opaque envelopes that were opened in the operating theatre just prior to the administration of SA. The study drug was prepared and coded by an anesthesiologist not involved in the study. The patient and the anesthesiology resident administering the TAP block and involved in data collection were also blinded to group assignment. The code was broken after the completion of the study and statistical analysis.

After written informed consent, patients were made familiar with 10 cm Visual Analog Scale (VAS) with 0 representing no pain and 10 representing worst imaginable pain before administering the block. Patients received a standard SA comprising hyperbaric 0.5% bupivacaine 1.8 ml with 25 μg fentanyl. TAP block was performed under all aseptic precautions, in the lumbar triangle of Petit bilaterally once the surgery had ended, and the sensory block had receded to T10 level by pin prick. A loss of resistance (LOR) to air technique was used to locate the TAP. An 18G disposable Tuohy needle (®B Braun) was inserted perpendicular to the sagittal plane, behind the mid-axillary line in the triangle of petit, and the fascial planes localized with LOR to air.[5] The first LOR indicated that the needle had pierced the external oblique aponeurosis and the second LOR indicated entry into the transversus fascial plane. Patients in Group B (control group) received 20 ml of 0.25% bupivacaine followed by 2 ml of 0.9% saline bilaterally, after negative aspiration for blood. Patients in Group BC (study group) received 20 ml of 0.25% bupivacaine followed by 1.0 μg/kg (total dose 2.0 μg/kg) of clonidine bilaterally. The clonidine dose was loaded in a separate 2 ml syringe in a volume made up to 2 ml with 0.9% saline for each side. After completion of the surgical procedure and block, patients were transferred to the postanesthesia care unit.

The duration of postoperative analgesia, defined as the time (in hours) from the giving of the TAP block to the time to the first analgesic request in the postoperative period was recorded. Degree of pain was observed using the VAS every 30 min for the first 2 h, then every hour for next 10 h and thereafter every 2 h till the patient demanded first dose of analgesia. The TAP block was deemed a failure if the patient requested analgesia within the first 2 h of administering the block, and the case was not included in analyses. Patients were given injection diclofenac 1 mg/kg intravenous (to a maximum of 3 mg/kg/day) on demand or if the VAS score was ≥3. Sedation was evaluated along with VAS using a four-point ordinal scale (1 = Wide awake and alert, 2 = Awake but drowsy, responding to verbal stimulus, 3 = Arousable, responding to physical stimulus, 4 = Not arousable, not responding to physical stimulus). The presence of sedation was defined as a sedation score >1 at any postoperative time point. A four point patient satisfaction score (1 = Extremely satisfied, 2 = Satisfied, 3 = Dissatisfied, 4 = Extremely dissatisfied) was also noted. Other associated side effects such as dryness of mouth, hypotension (systolic blood pressure <20% of baseline), and bradycardia (heart rate <60 bpm) were also observed. A note was made of the total analgesic consumption in the first 24 h after the block. All the observations were made by an anesthetist who was unaware of group allocation and blind to the study drug.

Outcome

The primary outcome was the duration of postoperative analgesia. Secondary outcomes were the total requirement of analgesics in the first 24 h postoperatively, patient satisfaction and possible clonidine side effects (dryness of mouth, sedation, hypotension, and bradycardia).

Sample size calculation

Based on 20 pilot cases done prior to the study, the duration of analgesia in Group B was 6.5 ± 1.1 h and 12.5 ± 4.5 h in Group BC. Sample size calculation based on this data had indicated that at least 25 patients in each group will be required to demonstrate a clinically significant difference (4 h) in the duration of postoperative analgesia with an $\alpha = 0.05$ and a power of 99%. However, 50 patients were recruited in each trial arm in an attempt to collect data on side effects.

Analysis

The data were compiled, tabulated, and statistically analyzed using SPSS version 17 (Chicago, IL, USA). Unpaired Student's t-test was used for analysis of duration of analgesia and VAS at the time of administration of injection diclofenac. For analysis of nonparametric variables, like the level of

sedation, and patient satisfaction score Mann–Whitney U-test was used. Results are presented as mean ± standard deviation. $P < 0.05$ has been considered significant.

Results

One hundred patients were enrolled and randomized for the study. One patient from Group B was excluded after randomization due to conversion to general anesthesia. Groups were comparable in terms of age and body mass index. The triangle of Petit was located easily on palpation, the transversus abdominis neuro-fascial plane was localized after one to two attempts, and the TAP block performed without complication in all patients. The TAP block failed in three patients in Group BC and in two patients in Group B. These patients were excluded from the analysis. Thus, a total of 47 patients each were analyzed in Groups B and BC. Duration of analgesia was significantly longer in group BC (17.8 ± 3.7 h; 95% confidence interval [CI]: 17-19 h) as compared to Group B (7.3 ± 1.15 h; 95% CI: 7-7.5 h; $P < 0.01$). Mean consumption of diclofenac was 150 mg (95% CI: 150 mg) and 65.4 mg (95% CI: 58-72 mg) in Groups B and BC ($P < 0.01$), respectively. All patients in Group BC were extremely satisfied ($P < 0.01$) while those in Group B were satisfied. Thirteen patients (28%) in Group BC were sedated but arousable ($P = 0.01$) compared to none in Group B. In Group BC, 19 patients complained of dry mouth as compared to 13 in Group B ($P = 0.121$). None of the patients experienced hypotension or bradycardia.

Discussion

This randomized, double-blind, controlled trial demonstrated that addition of clonidine to bupivacaine in single-shot TAP block for cesarean section under SA prolongs analgesia by 10-12 h and reduces overall postoperative analgesic requirements by more than 75 mg compared to bupivacaine alone.

Although long-acting neuraxial or patient-controlled epidural/IV opioids produce effective analgesia, they are frequently associated with nausea, vomiting, and pruritus, which reduce overall patient satisfaction.[6] In addition, hydrophilic opioids like morphine may cause delayed maternal respiratory depression due to rostral spread.[7] Use of neuraxial opioids may be limited by logistic issues and/or the presence of medical contraindications.[8,9] Systemically administered lipophilic opioids like pethidine may be secreted in breast milk and cause transient adverse neurobehavioral effects in the neonate.[10] Given these issues, there is considerable potential for a regional technique like TAP blockade to provide effective and long lasting postcesarean section analgesia.

Many previous investigators have reported the analgesic benefit of TAP block in patients undergoing a wide variety of lower abdominal surgeries.[1,2] including cesarean section,[11-13] but none of them have used clonidine as an additive to the local anesthetic. Belavy *et al.*[11] and McDonnell *et al.*[12] investigated the effect of TAP block with 0.5% ropivacaine 20 ml bilaterally in patients undergoing cesarean section and reported improved postoperative pain scores, reduced postoperative opioid consumption and higher patient satisfaction. In a recent study, Eslamian *et al.* concluded that bilateral TAP block with 0.25% bupivacaine decreases postoperative pain and analgesic consumption with a longer time to the first analgesic rescue.[14] A meta-analysis by Abdallah *et al.* concluded that TAP block can provide effective analgesia when spinal morphine is contraindicated or not used in patients undergoing LSCS under SA.[4]

However, a few investigators, who have used long-acting intrathecal opioids, have not found TAP block to be advantageous as a modality for the multimodal analgesic regimen.[3,15] This may be due to the limited duration of action of TAP block and the superiority of intrathecal morphine over a TAP block in relieving the visceral component of cesarean delivery pain.

A recent meta-analysis of randomized trials has demonstrated that the addition of clonidine to local anesthetics significantly prolongs the duration of the motor block and postoperative analgesia when used for peripheral nerve and plexus blocks.[16] The reason for the prolonged effect seen with clonidine is not clear because α2 adrenoreceptors are not present on the axon of the normal peripheral nerve.[17] Laboratory studies have suggested that clonidine exerts an effect directly on the nerve fiber, as a result of a complex interaction between clonidine and axonal inotropic, metabolic, or structure proteins (receptors).[18-21] Another hypothesis that may explain prolonged analgesia with clonidine is the systemic absorption of the drug from TAP.[22] This may explain sedation in 13 of the 47 patients in this group. Although the difference between the two groups was statistically significant, clinically, it was not relevant. Quite a few patients had been given a trial of labor and had prolonged labor pains. Also many were delivered at odd hours in the night. Although the patients were drowsy, they were responding to verbal commands and were able to breastfeed the babies. Thus, even with the use of clonidine, sedation did not in any way pose a clinical problem. Long hours of fasting and prolonged labor pains may have also contributed to dryness of mouth, which was comparable in the two groups. However, other systemic side effects of clonidine like bradycardia and hypotension were not observed. An extensive search of the literature revealed only one study describing the addition of clonidine to bupivacaine for TAP apart from ours. Bollag *et al.* evaluated wound hyperalgesia and long-term pain descriptors after cesarean delivery in women receiving an ultrasound guided bilateral TAP block with 0.375% bupivacaine with 75 μg clonidine on each side. They concluded that performing a TAP block with

or without clonidine does not appear to confer any benefits in wound hyperalgesia or analgesic consumption.[23]

There are a number of limitations of this study. First, was limited the assessment of PO analgesia to the time patient first demanded analgesia in the postoperative period. Second, the inter-group VAS was not compared at different time points, thus limiting the objective assessment of the quality of anesthesia. Third, the study was not large enough to assess safety. There is a risk of inadvertent peritoneal puncture with this block, however small. We, however, have not encountered this complication in the TAP blocks we now routinely perform. The use of ultrasound to confirm needle position further reduces the risk of this complication, besides increasing the success rate and efficacy of the block. But many centers, including ours, still do not have access to this facility. The patients who were unable to communicate either in English or Hindi were not enrolled for the trial, thus limiting the patient base. Finally, we did not perform a dose-response study to determine if a lower dose of clonidine would lead to the same results.

We conclude that addition of clonidine 1 μg/kg to 20 ml bupivacaine 0.25% in TAP block bilaterally for cesarean section provides 17-19 h of postoperative analgesia, decreases postoperative analgesic requirement, and increases maternal comfort compared to 20 ml of bupivacaine 0.25% alone with minimal side effects.

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