Local Infiltration of Tramadol versus Bupivacaine for Post Cesarean Section Pain Control: A Double-Blind Randomized Study

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Abstract

Background: Postoperative pain control after cesarean section (C/S) is important because inadequate postoperative pain control can result in a prolonged hospital stay. In this study, we compared postoperative somatic wound pain control between patients receiving tramadol and bupivacaine, infiltrated at the wound site.

Methods: In this randomized clinical trial, 98 patients, eligible for elective C/S under general anesthesia, were randomly allocated to 2 groups. Before wound closure, 20 cc of 0.025% bupivacaine and 2 mg/kg of tramadol, diluted to 20 cc, were infiltrated at the wound site in groups A and B, respectively. After surgery, the pain score was measured using the visual analogue scale (VAS). Additionally, 24-hour total morphine consumption, nausea and vomiting, and respiratory depression were compared after 2, 4, 8, 16, and 24 hours between the 2 groups. The data were analyzed using SPSS with the Student independent t test, χ² test, Fisher exact test, and repeated measure test.

Results: Postoperatively, there was no significant difference between these 2 groups in their VAS scores until 16 hours (P>0.05). However, at the 16th and 24th hours, the mean VAS scores were 3.20±2.24 and 2.51±2.55 in the bupivacaine group and 2.51±0.99 and 1.40±0.88 in the tramadol group, respectively (P<0.05). There was no difference in nausea and vomiting during the 24-hour period between the 2 groups. Also, no respiratory depression was detected in the both groups.

Conclusion: Local infiltration of tramadol (2 mg/kg) at the incision site of C/S was effective in somatic wound pain relief without significant complications.

Trial Registration Number: IRCT2013070111662N2

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Keywords ● Tramadol ● Bupivacaine ● Cesarean section ● Pain ● Postoperative

Introduction

The most common surgical procedure in women of childbearing age is cesarean section.¹ Adequate postoperative pain control is an important postoperative care in most procedures to reduce morbidity and mortality in patients.² Postoperative pain control assumes even greater importance after cesarean section because the patients are mothers who must be ready to nurse their babies as early as possible. In addition, it should
also be safe for neonates, who are being breastfed.3

Be that as it may, there seems to be no gold standard method for post caesarean pain management and several methods that are currently used include opioids, additional non-opioid painkillers, peripheral nerve block, and other supplementary techniques.4 Due to the complications of general anesthesia, nowadays, regional anesthesia is commonly used for cesarean section, which provides a route for postoperative analgesia through neuraxial opioids.5 However, each method has been investigated by several studies and each is proposed to have several advantages and disadvantages.6 Clinical studies have shown that wound infiltration with typical local anesthetics such as bupivacaine and ropivacaine, an effective post-cesarean analgesic agent after general anesthesia, reduces the severity of pain in the immediate postoperative period and have suggested that parenteral analgesics or local infiltration of anesthetic drugs constitute a proper postoperative pain management, especially when regional anesthesia is contraindicated.7,8

Tramadol is a methylmorphine with opioid analgesic action on the central nervous system, and several studies have demonstrated that tramadol may have a local anesthetic-type effect in minor operations,9 similar to that of lidocaine on the sodium channel of axons.10 Also, tramadol is proposed to be used as a local anesthetic to decrease the postoperative analgesic demand in major procedures such as cesarean delivery.11 Nevertheless, other aspects of tramadol, including complications in the central nervous system, have yet to be elucidated in cesarean section before tramadol infiltration can be safely suggested for this important procedure.

Thus, the aim of the present study was to compare the local anesthetic efficacy of tramadol with that of bupivacaine in controlling postoperative somatic wound pain following cesarean section under general anesthesia. In addition, the side effects of the drugs such as postoperative nausea and vomiting (PONV) and respiratory depression were compared between the 2 drug groups.

**Patients and Methods**

This randomized clinical trial (RCT) was a double-blind, placebo-controlled, parallel-group trial with a balanced randomization, performed in a single center. The study is registered in the Iranian Registry of Clinical Trials (IRCT2013070111662N2) and was approved by the institutional ethics committee. The study was conducted in the Obstetrics Operating Theater of Hafez Hospital, Shiraz, Iran, from January to June 2013. The purpose of the study was explained to the parturients and written informed consents were obtained from them.

The eligible participants were parturients aged between 20 and 40 years who were candidates for elective cesarean section under general anesthesia. The exclusion criteria of the study included parturients having a history of cardiopulmonary disorders, allergic reaction to the drugs used in the study, alcohol addiction, addiction to opium or other illicit drugs, chronic pain syndrome, neuropathic pain disorder, and seizure.

The eligible parturients were randomly assigned to 2 groups through block randomization; each block had 4 numbers and randomization was carried out by a computer-generated random sequence. Each of the parturients was allocated to 1 of the 2 parallel groups in a 1:1 ratio by a nurse anesthetist, who was not involved in the study. In Group A, 20 cc of 0.025% bupivacaine solution and in Group B, 2 mg/kg of tramadol, diluted to 20 cc, were infiltrated at the wound site at the end of surgery before wound closure. The bupivacaine and tramadol solutions were prepared by a nurse anesthetist, not related to the study, in 20-mL syringes that were identical in appearance. The syringes were labeled as A for 0.025% bupivacaine and B for tramadol (2 mg/kg), and the solutions each were diluted with normal saline to make up to a total volume of 20 mL. The patients and the research assessor were not aware of the contents of either syringe.

To decrease the risk of aspiration pneumonitis, we administered ranitidine and metoclopramide to all the patients 2 hours before the induction of anesthesia. In the operating room, after a complete airway evaluation for detecting difficult intubation, and if there was no sign of difficult intubation and if the parturient had demanded general anesthesia, she was made to lie on the operating table and the table was tilted 10 to 15° to the left. Then, standard monitors such as those for noninvasive blood pressure, ECG, and pulse oximetry were attached to the parturients. Thereafter, a suitable peripheral vein was cannulated with an 18-gauge angiocatheter. All the parturients in both groups received intravenous 0.9% saline (500 mL) and before the induction of anesthesia, they were pre-oxygenated with 6 L/min of 100% O₂ for 5 minutes. Anesthesia was induced via the rapid sequence technique with thiopental (5 mg/kg) and succinylcholine (1.5 mg/kg). Cricoid pressure/Sellick maneuver was applied.
from the time the patient became unconscious until endotracheal tube placement and cuff inflation were confirmed. Afterward, tracheal intubation was performed and anesthesia was maintained with 0.6% isoflurane and a 50% O₂–50% N₂O mixture with mechanical ventilation (tidal volume=6 mL/kg and respiratory rate=12/min). Cesarean section was performed by an obstetrician via a Pfannenstiel incision. After delivery and umbilical cord clamping, 30 U of oxytocin diluted in 0.9% saline (1000 mL) and 0.1 mg/kg intravenous morphine and 2 mcg/kg fentanyl were administered. Before skin closure and near the end of the surgery, in Group A, 20cc of 0.025% plain bupivacaine and in Group B, tramadol (2 mg/kg) diluted with physiologic saline to 20cc were infiltrated locally throughout the cesarean section wound site.

Outcome Measurements
The severity of postoperative somatic wound pain was the primary outcome with respect to the comparison between the efficacy of intracutaneous injection of tramadol and that of bupivacaine. Pain severity was measured using the visual analogue scale (VAS), which ranged from 0 (no pain) to 10 (worst pain imaginable). All the parturients were informed about the concept of the VAS. In the post-anesthesia care unit, if the VAS was >7, the patients received 2 mg of morphine intravenously every 5 minutes and if the VAS was between 4 and 7, the patients received 1 mg of morphine intravenously every 5 minutes until the VAS decreased to <4. In the obstetric ward, patient-controlled analgesia (PCA) was initiated with morphine. The PCA device used morphine with a 0.5-mg/mL concentration. The PCA was programmed as a bolus dose of 2 mL with a lock-out duration of 7 minutes and without basal infusion. In the postoperative period, a nurse, who was blinded to the study groups, asked the patients regarding their pain intensity with the VAS at 2, 4, 6, 16, and 24 hours after cesarean section.

The secondary outcomes were the total amount of morphine that each patient consumed through the PCA in the first 24 postoperative hours, respiratory depression, and PONV. Respiratory depression was defined as a respiratory <8 per minute.

A secondary outcome was the incidence of PONV, which was evaluated by asking the patients to grade their nausea and vomiting according to a 3-point scale: 0= no nausea, vomiting, 1= nausea only, and 2= retching and/or vomiting.

An anesthesiologist followed the non-blinded and presence of valvular heart disease (n=4), and presence of pulmonary disorders (n=2), a total of 12 parturients were excluded from the study due to pulmonary disorders (n=2), and valvular heart disease (n=4). Finally, 98 parturients were enrolled in this study.

Among the 250 patients, scheduled for elective cesarean section between January 2013 and June 2013, only 110 underwent general anesthesia for cesarean section. However, a total of 12 parturients were excluded from the study due to pulmonary disorders (n=2), a definite diagnosis of convulsion disorder (n=6), and presence of valvular heart disease (n=4). Finally, 98 parturients were enrolled in this study and were randomly allocated to control and intervention groups (figure 1).

There were no significant differences in the demographic data and mean operation time between the 2 groups (P>0.05) (table 1). The VAS scores were not significantly different between the study groups at 2, 4, and 8 postoperative hours (P>0.05). Nevertheless, the VAS scores in the tramadol group were significantly lower than those in the bupivacaine group at 16 and 24 hours postoperatively (figure 2). In addition, a repeated measure ANOVA was used to compare the VAS scores between the 2 groups and it showed that the VAS scores at different time points using the Student independent samples t-test. The Student independent samples t-test was employed to compare morphine consumption between the 2 groups. We also compared the mean VAS scores at different time points using the Student independent samples t-test.

Statistical Analysis
The study data were transferred into a computer database for statistical analysis using SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA). The numerical variables that were normally distributed were compared using the Student independent samples t-test. To compare the categorical variables such as PONV, we used the χ² test and the Fisher exact test. In addition, a repeated measure ANOVA was used to compare the VAS scores between the 2 groups. We also compared the mean VAS scores at different time points using the Student independent samples t-test. The Student independent samples t-test was employed to compare morphine consumption between the 2 groups. The statistical data are reported as means±SDs. Two-sided P<0.05 were considered statistically significant.

Results

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Scores in the tramadol group were significantly lower than those in the bupivacaine group at 16 and 24 hours postoperatively (P=0.003 and P<0.001, respectively) (table 2).

Furthermore, the consumption rates of morphine until the 16th postoperative hour were 0.26±0.04 mg/kg in the bupivacaine group and 0.24±0.04 mg/kg in the tramadol group, and the difference was not statistically significant (P=0.78). Nonetheless, from the 16th postoperative hour, morphine consumption was 0.21±0.03 mg/kg in the tramadol group, which was significantly less than that in the bupivacaine group (0.39±0.02) (P=0.001).

Moreover, no significant differences were observed in the incidence of PONV between the groups during different time points of the study (P>0.05) (table 3). In addition, respiratory depression was also not significantly different between the groups (P>0.05).

Discussion

The present study suggests that the local infiltration of tramadol throughout the wound was more effective than that of bupivacaine in reducing postoperative somatic wound pain intensity and analgesic requirement in parturients who underwent general anesthesia for cesarean section. Our results also demonstrated no respiratory depression in both groups.

Behdad and coworkers12 compared pain scores in 60 Iranian patients undergoing cesarean section receiving either a local wound infiltration of 10 mL of 0.5% bupivacaine or 50 mg of tramadol in 10 mL of normal saline randomly and found lower VAS scores in the tramadol group after 6 hours postoperatively with no difference in analgesic consumption or side effects. Although the doses of the analgesics in the present study differed from those in the study by Behdad and colleagues, the results were similar in terms of lower VAS scores and absence
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of side effects. Nevertheless, our findings revealed less analgesic consumption and lower VAS scores after 16 hours postoperatively in the tramadol group, which may have been due to the difference in the administered dosage of the analgesics. Similarly, in a study by Demiraran and colleagues,11 90 patients were randomized to receive a local wound infiltration of 20 mL of levobupivacaine, tramadol, or placebo and it was suggested that the tramadol group had lower VAS scores and that there was no significant difference between tramadol and levobupivacaine as regards analgesic (diclofenac) need, which was similar to the results of the present study, although the types of the procedures were different. Hence, they confirmed the advantage of the wound infiltration of tramadol over bupivacaine,13,14 which is in line with the present study.

Other studies have determined the efficacy of the local infiltration of tramadol in pain relief of other procedures such as hand surgery,9 adenotonsillectomy,15 and laparoscopic cholecystectomy,16 which confirms the results of the present study regarding the pain relieving efficacy of the local infiltration of tramadol.

The present study, also, demonstrated no respiratory suppression in both groups. Studies have suggested that the analgesic dose of tramadol induces little respiratory depression.17 In contrast, studies using the local infiltration of tramadol have reported no respiratory depression,12 which is confirmed by the results of the present study. Thus, it can be concluded that tramadol is a safe analgesic, when locally infiltrated. In addition, PONV after the administration of tramadol is commonly reported and its treatment is a challenging clinical issue.18 Be that as it may, in the present study, a comparison of PONV between the 2 groups showed that the local infiltration of tramadol did not increase PONV in comparison with bupivacaine. It can be concluded that tramadol has little PONV, when infiltrated locally. However, other studies using the local infiltration of tramadol have also stated similar PONV in patients receiving tramadol and bupivacaine.12

The strengths of the present study include the RCT nature of the study, which increases the reliability of the data, in addition to considering common side effects, which can confer researchers and clinicians a better view toward this issue. Yet, further studies are required to determine the optimal dosage of tramadol in cesarean delivery procedures, in addition to possible long-term outcomes. Furthermore, it would be more optimal to consider another group with intramuscular injection of tramadol in the study to compare the pain-reducing effect of tramadol with its local infiltration effect.

### Table 1: Demographic characteristics in the bupivacaine and tramadol groups

|                      | Bupivacaine Group (n=49) | Tramadol Group (n=49) | P value |
|----------------------|---------------------------|-----------------------|---------|
| Age (y)              | 26.7±3.95                 | 26.6±3.38             | 0.94    |
| Weight (kg)          | 66.8±5.18                 | 67.9±5.40             | 0.39    |
| BMI (kg/m²)          | 28.20±1.71                | 29.18±1.41            | 0.79    |
| Operation time (min) | 46.34±3.59                | 44.98±4.11            | 0.81    |

All data are means±SDs. BMI: Body mass index

### Table 2: Results of the repeated measurement of the VAS in the bupivacaine and tramadol groups

|                      | Bupivacaine Group (n=49) | Tramadol Group (n=49) | P value |
|----------------------|---------------------------|-----------------------|---------|
| VAS/2nd h            | 7.7±1.03                  | 7.7±1.41              | 0.85    |
| VAS/4th h            | 6.6±1.22                  | 6.6±0.93              | 0.92    |
| VAS/8th h            | 4.8±1.28                  | 4.46±0.98             | 0.11    |
| VAS/16th h           | 3.20±1.24                 | 2.51±1.00             | 0.003   |
| VAS/24th h           | 2.12±0.99                 | 1.140±0.88            | <0.001  |

All data are means±SDs. VAS: Visual analogue scale

### Table 3: Incidence of PONV in the bupivacaine and tramadol groups

|                      | Bupivacaine Group N/V (%) | Tramadol Group N/V (%) | P value |
|----------------------|---------------------------|------------------------|---------|
| PONV (2nd h)         | 7/1 (14.3/2)              | 8/2 (16.3/4.1)         | 0.56    |
| PONV (4th h)         | 6/1 (12.2/2)              | 6/3 (12.2/6.1)         | 0.78    |
| PONV (8th h)         | 10/0 (20.4/0)             | 7/1 (14.3/2)           | 0.64    |
| PONV (16th h)        | 5/0 (10.2/0)              | 1/0 (2/0)              | 0.71    |
| PONV (24th h)        | 2/0 (4.1/0)               | 0/0 (0/0)              | 0.59    |

All data are in numbers and percentages. PONV: Post-operative nausea and vomiting
Conclusion

In conclusion, the current study demonstrated that the local infiltration of tramadol (2 mg/kg) at the incision site of cesarean section was more effective than bupivacaine in somatic wound pain relief without significant complications. Thus, the local infiltration of tramadol throughout the cesarean section incision is proposed as a safe and effective post-cesarean analgesic after general anesthesia.

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