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ORIGINAL ARTICLE

Tramadol and levobupivacaine wound infiltration at Cesarean delivery for postoperative analgesia

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Abstract
Purpose The aim of the present study was to investigate whether levobupivacaine and tramadol wound infiltration decreases postoperative pain following Cesarean section and reduces the need for analgesics in the immediate post-delivery period.
Methods Ninety patients (aged 18–40 years) scheduled for elective Cesarean section under general anesthesia were randomly allocated to one of the three groups: the placebo group (group P) received 20 mL local wound infiltration with 0.9 % saline solution; the levobupivacaine group (group L) received 20 mL local wound infiltration with levobupivacaine 0.25 %; and the tramadol group (group T) received 20 mL local wound infiltration with 1.5 mg/kg tramadol within 0.9 % saline solution. Following the closure of the uterine incision and the rectus fascia, 20 mL solution was infiltrated subcutaneously along the skin wound edges. The primary outcome was 24-h tramadol consumption. Secondary outcomes were recorded VAS scores, diclofenac requirement, fever, vomiting, and wound infection.
Results At 15 min postoperatively, VAS values were lower in groups T and L than group P ($P = 0.0001$). The mean 24-h tramadol consumption was lowest in group T ($P = 0.0001$) and it was lower in the group L compared to group P ($P = 0.007$) (401.6, 483.3, and 557.5 mg for T, L, and P groups, respectively). There was no difference among groups regarding the need for supplemental analgesia (rescue diclofenac doses) ($P > 0.05$).
Conclusions We conclude that wound infiltration with tramadol and levobupivacaine in patients having Cesarean section under general anesthesia may be a good choice for postoperative analgesia.

Keywords Levobupivacaine · Tramadol · Postoperative analgesia · Infiltration

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Introduction

Cesarean section is a widely performed procedure and its rate varies among countries. Although spinal and/or epidural block are often the preferred anesthetic method in Cesarean delivery, the use of general anesthesia has its indications including emergencies such as fetal distress, various contraindications to neuraxial blocks, and patient request. Management of postoperative pain following Cesarean delivery under general anesthesia is mostly multimodal. Opioids have a sedating effect which may impair the early bonding process between mother and newborn [1]. A number of studies have reported the use of preemptive local anesthetics to relieve postoperative pain from several surgical procedures—including Cesarean delivery—with the results ranging from being beneficial [2, 3] to no benefit [4, 5].

Postcesarean delivery pain is mediated by somatic and visceral innervations. Analgesia of the subcutaneous tissue may increase the efficacy of postoperative analgesia and, to the best of our knowledge; this has not been explored in Cesarean deliveries. Previously, a low dose of 0.1 % ropivacaine was used as preemptive analgesia in women who underwent total abdominal hysterectomy [6]. Infiltration

local anesthesia is a well-accepted and safe anesthetic method for many surgical procedures. Combined with general anesthesia, local anesthetic infiltration can reduce the need for systemic analgesia [7]. Clinical studies have tested the efficacy of levobupivacaine in a wide spectrum of operations and anesthetic methods including local infiltration. The duration of action with local infiltration of levobupivacaine has been reported to be between 4 and 24 h [8, 9].

Tramadol is a weak opioid and selective for the μ receptors, and has recently been reported to have a local anesthetic action on peripheral nerves [10]. Pang et al. [11] observed a local anesthetic effect with intradermal injection of tramadol and lidocaine, and Tsai et al. [12] demonstrated a local anesthetic-type effect by possible neural conduction blockade by tramadol on sciatic nerves of rats. In a previous study of ours, we showed the postoperative analgesic effect of tramadol when used as subcutaneous local anesthetic [13].

The aim of the present study was to investigate whether levobupivacaine and tramadol wound infiltration decreases postoperative pain following Cesarean delivery under general anesthesia or reduce the need for analgesics in the immediate postoperative period.

Materials and methods

After obtaining approval from the Ethics Committee of our hospital and written informed consent from all participants, we studied 90 ASA physical status I–II patients scheduled for Cesarean delivery via a Pfannenstiel incision, in a randomized, double-blind, controlled clinical trial. The exclusion criteria were women who did not consent, history of previous local anesthetic events, hypertension in pregnancy with proteinuria, cardiac diseases, and any other major medical disorder associated with pregnancy.

The allocation sequence was generated by a random number table, and group allocation was concealed in sealed, opaque envelopes that were not opened until patient consent had been obtained. The patients, their anesthesiologists, and staff providing postoperative care were blinded to group assignment. The patients were randomly allocated to one of the three groups: the placebo group (group P) ($n = 30$) received 20 mL local wound infiltration with 0.9 % saline solution; the levobupivacaine group (group L) ($n = 30$) received 20 mL local wound infiltration with levobupivacaine 0.25 %; and the tramadol group (group T) ($n = 30$) received 20 mL local wound infiltration with tramadol 1.5 mg/kg within 0.9 % saline solution. All local wound infiltrations were performed at the end of surgery by the same operator. For the surgical procedure, Pfannenstiel incisions were done under general anesthesia. For each woman, a lower segment Cesarean delivery was performed, the neonate was delivered, intravenous oxytocin was given, and the placenta was delivered by cord traction. Following the closure of uterine incision and the rectus fascia, a previously prepared 20 mL solution was infiltrated subcutaneously along the skin wound edges and the skin approximated with a subcutaneous absorbable 3-0 polyglecaprone suture.

During the preoperative visits, the patients were introduced to the concept of the visual analogue scale (VAS), which ranged from 0 = no pain to 10 = worst pain imaginable. On arrival in the operating room (OR), standard monitoring was applied with automated noninvasive blood pressure measurement, electrocardiography, and pulseoximetry. Baseline data collection was started when the patient had been settled on the OR table in preparation for general anesthesia. Anesthetic induction was achieved with 4–6 mg/kg thiopental, 0.5 mg/kg atracurium in all groups while maintenance was with 1.5–2 % sevoflurane and 50 % N_2O–50 % O_2 mixture at 5 L/min. At the end of surgery, the patients were extubated and taken to the recovery room. Perioperative conditions were similar in the three groups. Intraoperative and postoperative assessment was performed by an investigator blinded to the patients' group. The patients' pain was evaluated with VAS as soon as they were responsive to verbal stimuli and patient-controlled analgesia (PCA) was initiated with tramadol. The PCA device (Abbott Pain Management Provider, North Chicago, IL, USA) was programmed as loading dose: the total of repeated 20-mg bolus doses every 3 min until VAS $\leq$3, basal infusion rate: 5 mg/h, bolus dose: 20 mg, and duration of lock out: 15 min. Patients evaluated the intensity of their pain with the VAS scale during rest and movement for a total of 8 times, starting as soon as they responded to verbal stimuli in the recovery room (15 min) and at postoperative 2, 4, 8, 12, 16, 20, and 24 h. VAS $\leq$3 was considered to be an adequate level of analgesia. The bolus dose was increased to 25 mg in patients with VAS >3 and, if it was still not possible to provide an adequate level of analgesia, 75 mg intravenous diclofenac was used as an additional analgesic. The primary outcome measure in this study was 24-h tramadol consumption. Secondary outcomes were recorded, i.e. VAS scores, diclofenac requirement, fever, vomiting, and wound infection.

For the purposes of sample size calculation, we assumed that a clinically important reduction in 24-h tramadol consumption would be a 25 % absolute reduction. Based on initial pilot studies, we projected a mean 24-h tramadol requirement of 550 mg with a standard deviation of 75 mg in the control group. We calculated that 25 patients would be required per group for an experimental design incorporating three equal sized groups ($\alpha = 0.05$, $\beta = 0.2$). To minimize any effect of data loss, we elected to recruit 30

patients per group into the study. Non-parametric tests were used for the statistical analyses of the group comparisons due to the distribution characteristics of the compared variables. The Wilcoxon test was used for inter-group comparisons and a P value <0.05 was considered significant. The inter-group nominal values and side effects were compared with the Chi square or Fisher's Exact test while the Mann–Whitney U test was used to compare the inter-group numerical values, and a P value <0.05 was considered significant.

Results

There were no differences among groups regarding age, weight, height, or history of previous Cesarean section (Table 1).

At 15 min postoperatively, VAS values were lower in groups T and L than group P ($P = 0.0001$). There was no difference at 2, 4, 8, 12, 16, 20, and 24 h among groups ($P > 0.05$) (Table 2).

The mean 24-h tramadol consumption was lowest in group T ($P = 0.0001$) and it was lower in the group L compared to group P ($P = 0.007$) (401.6, 483.3, and 557.5 mg for T, L, and P groups, respectively) (Table 3). There was no difference among groups regarding the need for supplemental analgesia (rescue diclofenac doses) ($P > 0.05$) (Table 3).

Side effects encountered during the treatment are presented in Table 3. The most common side effect was vomiting in all groups, followed by pruritus. Four patients from group P, 5 patients from group T, and 5 patients from group L required intervention for vomiting ($P > 0.05$). Two patients from group P, 3 patients from group T, and 2 patients from group L required no intervention for mild pruritus ($P > 0.05$). Fever above 38 °C was not observed in any of the patients in group P. One patient from group T and 2 patients from group L required intervention for fever above 38 °C ($P > 0.05$). Wound infection was not observed in groups T and L. One patient from group P required intervention for wound infection ($P > 0.05$) (Table 3).

Table 1 Baseline characteristics of women allocated to all groups during elective Cesarean delivery under general anesthesia

Characteristics	Group P ($n = 30$)	Group T ($n = 30$)	Group L ($n = 30$)	P values
Age (year)	27.8 ± 5.2	26.5 ± 4.4	25.6 ± 4.7	>0.05
Weight (kg)	79.5 ± 10	77.7 ± 9.3	80.6 ± 10.2	>0.05
Height (cm)	160.9 ± 4	161 ± 5.1	162 ± 3.8	>0.05
Primary Cesarean	23 (76 %)	24 (80 %)	22 (73 %)	>0.05
Nulliparous	18 (60 %)	17 (56 %)	20 (66 %)	>0.05

Values are given as means and number of cases (percentage) unless otherwise specified

Table 2 VAS values at different time intervals

Time	Group P ($n = 30$)	Group T ($n = 30$)	Group L ($n = 30$)	P values
VAS 15 min (rest)	7.7 ± 1.8	4.6 ± 1.3[a]	4.5 ± 1.3[a]	0.001
VAS 2 h (rest)	2.7 ± 1.3	2.2 ± 1.2	2.6 ± 1.7	>0.05
VAS 4 h (movement)	1.7 ± 1.0	2.0 ± 1.4	1.8 ± 1.2	>0.05
VAS 8 h (movement)	1.5 ± 1.3	1.6 ± 1.3	1.5 ± 1.1	>0.05
VAS 12 h (movement)	1.5 ± 1.3	1.7 ± 1.5	1.4 ± 0.9	>0.05
VAS 16 h (movement)	0.9 ± 0.5	1.4 ± 1.2	1.0 ± 0.6	>0.05
VAS 20 h (movement)	1.0 ± 1.1	1.2 ± 1.2	0.7 ± 0.6	>0.05
VAS 24 h (movement)	0.4 ± 0.5	0.7 ± 0.7	0.4 ± 0.5	>0.05

Values are given as mean ± SD

[a] According to control group, significant at $P = 0.001$

Table 3 Total analgesic consumption at 24 h (tramadol), rescue diclofenac dose required and complications

	Group P ($n = 30$)	Group T ($n = 30$)	Group L ($n = 30$)	P values
Tramadol 24 h (mg)	557.5 ± 76.9	401.6 ± 105.3[a,b]	483.3 ± 120[a]	0.001
Rescue diclofenac (mg)	17.5 ± 32.2	10 ± 25.9	17.5 ± 32.2	>0.05
Pruritus	2	3	2	>0.05
Vomiting	4	5	5	>0.05
Temp. above 38 °C	0	1	2	>0.05
Wound infection	1	0	0	>0.05

[a] Among all groups, significant at $P = 0.001$

[b] Between groups T and L, significant at $P = 0.007$

Discussion

The analgesic efficacy of subcutaneous wound infiltration with 20 mL of levobupivacaine 0.25 %, tramadol, and saline after elective lower segment Cesarean section was studied in 90 patients in a double-blind randomized controlled manner using a patient-controlled analgesia system. The mean 24-h tramadol consumption of the placebo group, the tramadol group, and the levobupivacaine group were different (557.5, 401.6, and 483.3 mg, respectively).

In the present study, we observed that the wound infiltration with tramadol and levobupivacaine decreased postoperative analgesic consumption. Additionally, VAS values at 15 min in the levobupivacaine and tramadol groups were significantly lower than in the placebo group.

Patients undergoing Cesarean section require a perioperative analgesic technique that is effective, has minimal side effects, is intrinsically safe, and continues to provide analgesia after discharge from the recovery room. The adequacy of postoperative pain control is one of the most important factors in determining when a patient can be safely discharged from the recovery room. Opioids provide good pain relief particularly in severe pain. However, their use is restricted because of potential side effects. Nevertheless, the use of local anesthetic agents may also avoid many of the potential problems associated with opioids [14].

Clinical studies have shown that tramadol had peripheral local anesthetic-type properties [12, 13, 15]. Altunkaya et al. [15] showed that the duration of postoperative analgesia provided by subcutaneous tramadol was significantly longer compared with lidocaine [15]. In our previous study, the duration of postoperative analgesia provided by wound infiltration with tramadol was significantly longer compared with either bupivacaine injection or IM (intramuscular) tramadol. Wound infiltration with tramadol achieved approximately 2 h longer analgesia than IM tramadol. This indicates that analgesia is achieved by a local effect rather than systemic absorption, as occurs in the IM group [13]. In the present study, we observed decreased postoperative analgesic consumption with wound infiltration of tramadol and VAS values at 15 min in the tramadol group was significantly lower than in the placebo group.

Local analgesic infiltration and abdominal nerve blocks as adjuncts to regional analgesia and general anesthesia are of benefit in Cesarean section by reducing opioid consumption. Nonsteroidal anti-inflammatory drugs as an adjuvant may confer additional pain relief [16]. Pavy et al. [17] suggests that preoperative skin infiltration with 0.5 % bupivacaine may provide reduced postoperative pain. Ropivacaine wound infiltration and peritoneal spraying as preemptive postoperative analgesia in Cesarean delivery under general anesthesia reduces the need for narcotics and analgesics, and reduces severe pain in the immediate postoperative period [18]. Clinical studies have tested the efficacy of levobupivacaine in a wide spectrum of operations and anesthetic methods including local infiltration. The duration of action has been reported to be between 4 and 24 h with local infiltration of levobupivacaine [7–9]. In our previous study, we compared the use of preincisional lidocaine 2 % with epinephrine and levobupivacaine 0.25 % for postoperative analgesia in patients undergoing nasal septal surgery, and reported that local infiltration of levobupivacaine was significantly more effective for long-term postoperative analgesia [7]. In our present study, we observed decreased postoperative analgesic consumption in wound infiltration with levobupivacaine and VAS values at 15 min in the levobupivacaine group was significantly lower than in the placebo group.

There were no allergic, cardiovascular, or central nervous system side effects among the levobupivacaine- and tramadol-exposed women. To the best of our knowledge, there is no study addressing the levobupivacaine and tramadol doses in wound infiltration at Cesarean delivery under general anesthesia, and this may serve as a guide for such cases or future trials.

In conclusion, postoperative analgesia was significantly prolonged and fewer analgesics were required after wound infiltration with tramadol or levobupivacaine at Cesarean section under general anesthesia. We conclude that this technique may be a good choice for postoperative analgesia in patients having Cesarean section under general anesthesia.

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