COMPARISON OF POSTOPERATIVE ANALGESIC EFFECT OF TRAMADOL AND BUPIVACAINE SUBCUTANEOUS INFILTRATION IN PATIENTS UNDERGOING CESAREAN SECTION

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SUMMARY – Cesarean section is associated with significant postoperative pain. The aim of this study was to evaluate the effects of tramadol *versus* bupivacaine administration at wound closure on postoperative pain relief in patients undergoing cesarean section. Sixty women undergoing cesarean deliveries were randomly assigned to receive either 10 mL of bupivacaine 0.5% (n=30) or 50 mg of tramadol in 10 mL of normal saline (n=30), both as local wound infiltration prior to skin closure at the end of operation. Postoperative pain was evaluated with a visual analogue scale (VAS: 0-10) at 1, 2 and 6 hours after operation. Time to first analgesic administration and analgesic consumption in 24 hours after operation were recorded and compared between the two groups. Data were analyzed by SPSS software version 15 and $p<0.05$ was considered significant. The VAS score did not differ significantly between the two groups at 1 and 2 hours after cesarean section, but it was higher in bupivacaine group than tramadol group 6 hours after operation ($p<0.05$; Fisher exact test). Postoperative consumption of analgesic was higher in bupivacaine group than tramadol group but the difference was not significant ($p>0.05$; Fisher exact test). No side effects were reported in either group. This study showed that subcutaneous administration of tramadol provided analgesic effect equal to bupivacaine with longer pain relief after cesarean section.

Key words: *Postoperative analgesia; Cesarean delivery; Postoperative pain; Bupivacaine; Tramadol*

Introduction

The management of postoperative pain has received much interest in recent years. The intensity of postoperative pain, as ultimately perceived by the patient, is multifactorial and depends on variables such as type and duration of the operation, type of anesthesia and analgesia used, and the patient's mental and emotional status[1]. There are many methods of postoperative pain treatment[2-4]. Parenteral narcotics as the traditional method in general are associated with nausea, vomiting, constipation, respiratory depression, and sedation[2]. Newer technologies, such as continuous epidural analgesia or patient-controlled analgesia, have adverse effects, are expensive, and require trained personnel and special equipment[3]. Another option for postoperative pain management is to administer oral analgesics immediately after the procedure[4].

Cesarean delivery is the most frequent major surgical procedure in obstetrics[5], and is unique in that the patient must recuperate from surgery while caring for a newborn infant[6]. The provision of effective postoperative analgesia is of key importance to facilitate early

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ambulation, infant care and prevention of postoperative morbidity[7]. The analgesic regimen needs to meet the goals of providing safe, effective analgesia, with minimal side effects for the mother and her child. So, it would be of great value to optimize the post-cesarean pain treatment. Recent works suggest that pre- and postoperative skin infiltration with local anesthetic may lead to reduced post-cesarean pain[6,8-10].

Tramadol is a weak opioid and selective for the N receptors, and is a centrally acting drug, which is effective in the treatment of moderate to severe pain. In addition to its systemic action, the local anesthetic effect of tramadol on peripheral nerves has been shown in both clinical and laboratory studies[11]. Its analgesic effects are mediated by at least three different mechanisms: it is a weak μ opioid receptor agonist; it inhibits the reuptake of the neurotransmitters hydroxytryptamine (5cHT) and norepinephrine in the descending inhibitory pain pathways, and facilitates 5cHT release[11,12].

The aim of this study was to evaluate the effect of tramadol on the degree of postoperative pain and amount of postoperative analgesic consumed in comparison to bupivacaine.

Subjects and Methods

After institutional research and ethics committee approval, this prospective, double-blind, placebo-controlled, randomized clinical trial was designed and conducted in 60 women undergoing elective cesarean delivery in Shahid Sadoughi Hospital, Yazd, Iran, from April 2011 to March 2012. These patients were chosen among some 1000 patients who underwent cesarean section in this period. All women were interviewed individually by the researcher. Written informed consent was obtained from all patients.

Sample size estimations were based on the results of a previous study, and assuming an α level of 0.05 and ß error of 0.8; 27 patients were needed *per* group to detect a one-point difference on the 0 to 10 visual analog pain scale score. To account for the possible loss to follow-up, it was decided to include 30 patients *per* trial arm.

Women were excluded from the study if they had a known allergy/hypersensitivity to tramadol, systemic diseases (cardiopulmonary disease, diabetes, and hypertension), neurologic disorder, preeclampsia and chronic use of narcotics or substance abuse. The patients were randomly allocated to either tramadol group or bupivacaine group (30 women each). Randomization was performed with a computer-driven random number sequence and sealed in opaque envelopes. Prior to each operation, the surgeon was provided with a syringe containing 50 mg of tramadol (Exir Pharmaceutical Co.) in 10 mL normal saline in the tramadol group or 10 mL of bupivacaine (Mylan Technologies Inc.) 0.5% in the bupivacaine group, which was injected subcutaneously in the line of the incision before skin closure at the end of operation. All 60 syringes with solutions were prepared by the pharmacy department and their contents were determined by random numbers generated by a computer. The codes of the solutions were disclosed for the investigators only upon completion of statistical analysis of the results. After disclosure of the codes, it was found which women had received tramadol and which had been treated by bupivacaine.

All cesarean sections were performed under general anesthesia because of the patients' preferences. Induction and maintenance of anesthesia were the same for all patients in the two groups. General anesthesia was induced using thiopental (Kwality Pharmaceuticals PVT Ltd.) 5 mg/kg, and succinylcholine (Biologici Italia Laboratories, B.I.L.) 1-1.5 mg/kg; 0.5 MAC isoflurane and 50% O_2 and 50% N_2O were used for maintenance of anesthesia. Atracurium (0.5 mg/kg) was given for muscle relaxation during anesthesia. At the end of surgery, muscle relaxation was antagonized by prostigmine (0.04 mg/kg) and atropine (0.02 mg/kg). All skin incisions were Pfannenstiel and Kerr incision used for uterine procedures; after delivery, the site of surgery was closed by subcutaneous suture by coated vicryl (polyglactin 910) 3/0. After fetal delivery, 2 μg/kg fentanyl (Mylan Technologies Inc.) was administered to each woman as a routine. Following surgery, all women were treated in the postoperative care unit for 2 hours. One to two L of lactated Ringer's solution was administered during the operation in all patients. They were closely monitored in the recovery room.

Postoperative pain was evaluated with a visual analogue scale (VAS: 0-10) at 1, 2 and 6 hours after operation. The self-report of pain is assessed by the patient on a validated 10-cm VAS, as instructed by

the nursing staff. This pain scale provides a validated and minimally intrusive measure of pain intensity; the scale ranges from "no pain" (0) to "the most severe pain imaginable"(10). Patients were instructed to place a mark on the line that indicated the level of pain experienced. The distance in centimeters from the lower end of the VAS and the patient's mark was used as a numerical index of pain intensity. The questionnaires were filled out for each patient at the beginning of the study and after operation. If the VAS score was greater than 6, then 30 mg pentazocine (Tolid Daru Pharma Co.) was injected intramuscularly and time of first administration and total doses of analgesia requirements in the first 24 hours after operation were recorded. If there was any side effect in either group, it was recorded and compared.

Analysis of data was performed with the SPSS 15.5 software. Statistical methods included Student's t-test and Fisher exact test. The value of P<0.05 was considered statistically significant.

Results

Sixty women completed the study. Thirty women received analgesia with tramadol and bupivacaine 0.5% each. Table 1 shows that there was no difference in demographic and medical characteristics of the two study groups. As a result of the study design, the two study groups were also identical according to indications for cesarean section. No adverse reactions were noted following local injection in either group.

Table 2 presents the main data on the postoperative analgesic treatments and pain assessments. As for VAS score, there was no significant difference between the groups in the pain scores at 1 and 2 h after operation (5.13±0.93 *vs*. 5.53±1.52 and 5±1.17 *vs*. 5.57±1.22 in tramadol group and bupivacaine group respectively, *P*>0.05). The patients' pain scores at 6 h were significantly lower in tramadol group than bupivacaine group (3.83±1.08 in tramadol group *vs*. 4.73±1.25 in bupivacaine group, *P*=0.004). The mean time of first analgesic requirement was earlier in bupivacaine group than tramadol group, but the difference was not statistically significant (6.6±3.98 *vs*. 4.66±3.66 h in tramadol and bupivacaine group, *P*= 0.04). The number of patients requiring supplemental analgesics in the first 24 h was 11 in tramadol group and 20 in bupivacaine group (*P*=0.006)

Total Talvin consumption was lower in patients who had received subcutaneous wound infiltration with tramadol compared with those who had received bupivacaine (*P*=0.03).

Table 1. Maternal characteristics of study groups (t-test)

Characteristic	Tramadol (n=30)	Bupivacaine (n=30)	*P* value (t-test)
Age (yrs) (mean ± SD)	26.7±5.1	28.1±7.9	0.51
Parity (number (%))			
primi	12 (40)	10 (33.3)	0.30
multi	18 (60)	20 (66.7)	
Gestational age (wks) (mean ± SD)	38.6±1.3	38.4±1.6	0.20
Indication (n (%))			
repeated	19 (63.3)	16 (53.4)	0.20
CPD	5 (16.7)	7 (23.3)	
other	6 (20)	7 (23.3)	
Operative time (min) (man ± SD)	60.4±15.3	61.8±16.8	0.39
Length of hospital stay (h) (mean ± SD)	60.1±8.2	62.3±9.1	0.24

CPD = cephalopelvic disproportion

Table 2. Postoperative analgesic treatment and pain assessment in study groups by VAS score (t-test)

	Tramadol (n=30)	Bupivacaine (n=30)	*P* value (t-test)
Pain score 1 h of surgery (mean ± SD)	5.13±0.93	5.53±1.52	0.12
Pain score 2 h of surgery (mean ± SD)	5±1.17	5.57±1.22	0.11
Pain score 6 h of surgery (mean ± SD)	3.83±1.08	4.73±1.25	0.004
Mean time to first analgesic requirement (h) (mean ± SD)	6.6±3.98	4.66±3.66	0.04
Patients requiring more analgesia in the first 24 h (n (%))	11 (36.67)	20 (66.67)	0.006
Total Talvin consumption in the first 24 h (mg) (mean ± SD)	42.9±24.3	37.8±17.4	0.03

Table 3 shows side effects in the two study groups. Postoperative nausea occurred in six women in tramadol group and eight women in bupivacaine group (*P*=0.37), and vomiting in four women in tramadol group and seven women in bupivacaine group (*P*=0.23). There was no case of hypotension or cardiovascular complications.

Table 3. Drug side effects in study groups in the first 24 h (Fisher exact test)

Side effect	Tramadol (n = 30)	Bupivacaine (n = 30)	*P* value (Fisher exact)
Nausea (n (%)	6 (20)	8 (26.7)	0.37
Vomiting (n (%)	4 (13.3)	7 (23.3)	0.23
Hypotension (n %)	0	0	-
Cardiovascular	0	0	-

Discussion

This study showed that subcutaneous administration of tramadol provided analgesic effect equal to bupivacaine and with longer pain relief after cesarean section. Moreover, total excess analgesic consumption was lower in patients who had received subcutaneous wound infiltration with tramadol compared with those who had received bupivacaine. Nausea and vomiting were the major side effects of tramadol used for postoperative analgesia; however, in our study these side effects were not more pronounced with tramadol as compared with bupivacaine.

Local anesthetic instillation into surgical wounds was found to be effective in many studies[8,13-15]. Initially, it was thought that tramadol produced its antinociceptive and analgesic effects through spinal and supraspinal sites rather than *via* a local anesthetic action, but clinical studies have shown that tramadol has a local anesthetic effect[11,14,15]. We studied the local anesthetic and postoperative analgesic effects of tramadol given subcutaneously after cesarean section and tramadol had a local anesthetic action similar to that of bupivacaine. Some studies used analgesic drug subcutaneously after cesarean section.

In contrast to our study, Altunkaya *et al.* compared tramadol and prilocaine as local anesthesia and report that intradermal tramadol can provide local anesthesia similar to prilocaine but the incidence of local adverse effects was higher[11].

Because there was no previous study evaluating the use of tramadol as a local anesthetic in cesarean section, this study was a new experience. So, we did not have a reference dose. We gave 50 mg tramadol (which was used safely by intramuscular injections for analgesia).

Conclusion

This study showed that subcutaneous infiltration of tramadol provided analgesic effect equal to bupivacaine but with longer pain relief after cesarean section. We conclude that tramadol may be a good choice for local anesthesia after surgery.

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Sažetak

USPOREDBA POSLIJEOPERACIJSKOG ANALGEZIJSKOG UČINKA POTKOŽNE PRIMJENE TRAMADOLA I BUPIVAKAINA U BOLESNICA PODVRGNUTIH CARSKOM REZU

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Carski rez je udružen sa značajnom poslijeoperacijskom boli. Cilj ove studije bio je procijeniti učinak primjene tramadola u usporedbi s bupivakainom pri zatvaranju rane na olakšanje poslijeoperacijske boli u bolesnica podvrgnutih carskom rezu. Po 30 od ukupno 60 žena podvrgnutih carskom rezu i uključenih u studiju nasumce je primilo 10 mL bupivakaina 0,5% ili 50 mg tramadola u normalnoj fiziološkoj otopini ukapljeno u operacijsku ranu prije zatvaranja rane na kraju zahvata. Poslijeoperacijska bol procjenjivala se pomoću vizualne analogne ljestvice (VAS: 0-10) 1, 2 i 6 sati nakon operacije. U obje skupine bilježilo se i usporedilo vrijeme do prvog davanja analgetika i potrošnja analgetika kroz 24 sata od operacije. Podaci su analizirani pomoću programa SPSS ver. 15, a razina statističke značajnosti utvrđena je kao $P<0,05$. Zbir na ljestvici VAS nije se značajno razlikovao među skupinama 1 i 2 sata nakon carskog reza, ali je nakon 6 sati bio viši u skupini koja je primila bupivakain negoli u skupini koja je primila tramadol ($P<0.05$; Fisherov egzaktni test). Poslijeoperacijska potrošnja analgetika bila je veća u skupini koja je primila bupivakain nego u skupini koja je primila tramadol, ali razlika nije bila značajna ($P>0.05$; Fisherov egzaktni test). Ni u jednoj skupini nisu zabilježene nikakve nuspojave. Ova studija je pokazala da potkožna primjena tramadola ima jednak analgezijski učinak kao bupivakain, ali s dužim olakšanjem boli nakon carskog reza.

Ključne riječi: *Poslijeoperacijska analgezija; Carski porođaj; Poslijeoperacijska bol; Bupivakain; Tramadol*