THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2018.19327
Med Bull Sisli Etfal Hosp 2019;53(1):16–20

Research Article

# Evaluation of Anesthetic and Analgesic Effects of Intrathecal Administration of Tramadol vs Fentanyl

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## Abstract

**Objectives:** The aim of this study was to examine the anesthetic and analgesic effects of intrathecal tramadol compared with intrathecal fentanyl added to bupivacaine and that of a placebo added to bupivacaine in patients undergoing elective transurethral procedures.

**Methods:** The anesthetic and analgesic efficacy of intrathecal tramadol hydrochloride (HCL) was assessed against a local anesthetic in this prospective, double-blind, randomized study of 146 American Society of Anesthesiologists classification I-III patients who underwent an elective transurethral procedure. A lumbar intrathecal block was performed using bupivacaine heavy 0.5 % combined with either tramadol HCL, fentanyl, or saline for surgery. Each group received 12.5 mg bupivacaine with 50 µg (1 mL) fentanyl, 12.5 mg bupivacaine with 10 mg (1 mL) tramadol, or 12.5 mg bupivacaine with 1 mL preservative-free saline.

**Results:** The saline group experienced more pain than patients in the tramadol HCL and fentanyl groups ($p<0.05$). The mean time to regression of the sensory block to the S1-2 segment was significantly longer in the fentanyl group compared with the tramadol and saline groups ($p<0.05$). The incidence of complications was similar.

**Conclusion:** Fentanyl added to a local anesthetic provided longer postoperative analgesia compared with tramadol added to a local anesthetic.

**Keywords:** Intrathecal anesthesia; local anesthetic; tramadol hydrochloride.

Please cite this article as "Özer S, Türk HŞ. Evaluation of Anesthetic and Analgesic Effects of Intrathecal Administration of Tramadol vs Fentanyl. Med Bull Sisli Etfal Hosp 2019;53(1):16–20".

Several adjuvant drugs may be combined with local anesthetics to prolong a sensorial block and to provide longer postoperative analgesia after spinal anesthesia.[1] The duration of analgesia after a surgical procedure performed using intrathecal opioid administration with regional anesthesia has been evaluated.[2]

Tramadol hydrochloride (HCL) is a centrally acting analgesic drug consisting of 2 enantiomers, contributing analgesic activity via µ-opioid receptor agonism and monoaminergic mechanisms. In vivo and in vitro studies have proven that tramadol has a low but preferential activity at µ opioid receptors, inhibits both noradrenaline and 5- hydroxytryptamine (5-HT) neuronal reuptake, and facilitates 5-HT release.[3, 4] Tramadol has a low affinity for opioid receptors, but its analgesic potential is only 5 to 10 times less than that of morphine, and the analgesic potency can be equal to the potency of pethidine.[5, 6] In addition, tramadol has not been associated with clinically significant respiratory depression; there appears to be a low potential for the development of tolerance, dependence, or abuse; and unlike

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**Submitted Date:** February 15, 2018 **Accepted Date:** March 17, 2018 **Available Online Date:** March 21, 2019

morphine, it does not elicit a histamine release and so does not cause skin flushing or idiosyncratic hypotension.[7, 8]

Intravenous administration and the almost opioid-equal efficacy of tramadol is familiar to anesthetists.[9] It was reported to increase bladder capacity and compliance without any significant ill effect on voiding, whereas opioids caused urinary retention.[10] There are several animal studies using intrathecal tramadol. Studies on rats demonstrated that intrathecal tramadol caused a dose-related suppressive effect on both sensory and motor neuronal conduction in the spinal cord, and that intrathecal tramadol produced analgesia in a tail flick model.[11, 12] A few studies have compared intrathecal fentanyl and tramadol, and they were found to produce similar analgesic activity.

Opioids are popular adjuvants for local anesthesia sue to the prolonged analgesic effects, but the potential side effects of intrathecally administered opioids include respiratory depression, nausea, vomiting, and pruritus.[13, 14] Comparative studies have indicated that intrathecal tramadol resulted in fewer adverse effects than fentanyl.

This study was designed to observe the anesthetic and analgesic effects of intrathecal tramadol and intrathecal fentanyl added to bupivacaine compared with a placebo added to bupivacaine on patients undergoing elective transurethral procedures.

## Methods

After approval from the institutional ethics committee of Sisli Hamidiye Etfal Education and Research Hospital 28.05.2005/34, written informed consent was obtained from the patients for this randomized, double-blind, placebo-controlled clinical trial. The study was conducted in accordance with the Declaration of Helsinki. A total of 146 patients between the ages of 18 and 71 years and with an American Society of Anesthesiologists classification of between I and III who were to undergo an elective transurethral procedure were eligible for the study. Patients with contraindications for spinal anesthesia or an allergy to the study drugs were excluded. A computer-generated randomization program allocated the patients into 3 groups: Group F, which received intrathecal bupivacaine heavy 0.5% 12.5 mg (2.5 mL) (Marcaine Spinal Heavy 0.5%; Hospira, Inc., Lake Forest, IL, USA) and fentanyl citrate 50 µg (1 mL) (Fentanyl Citrate; Abbott Laboratories, Abbott Park, IL, USA), Group T, which was given intrathecal bupivacaine heavy 0.5% 12.5 mg (2.5 mL) (Marcaine) and tramadol HCL 10 mg (1 mL) (Contramal; Grunenthal GmbH, Aachen, Germany), and Group S, which received intrathecal bupivacaine heavy 0.5 % 12.5 mg (2.5 mL) (Marcaine) and preservative free saline 1 mL.

No premedication was administered to any patient. In the operating room, all of the patients were hydrated with an intravenous bolus of 8 to 10 mL kg-1 lactated ringer solution after the application of the standard monitors. Heart rate (HR) and mean arterial blood pressure (BP) were recorded at baseline and every 5 minutes for 20 minutes after the intrathecal injection and at every 15 minutes thereafter until the end of surgery. Baseline values were obtained immediately before the procedure. Respiratory rate was recorded every 15 minutes throughout the study and oxyhemoglobin saturation was monitored using pulse oximetry in all patients for 1 hour after the intrathecal injection.

Antisepsis of the patient's lumbar skin was performed, and an 11-cm 25-G pencil-point spinal needle was inserted into the intrathecal space at either the L2-3 or the L3-4 interspace via a midline approach while the patient was in the sitting position. After observing free cerebrospinal fluid outflow of 3.5 mL, the intrathecal injection was administered over 60 seconds in a blinded fashion. After the procedure, the patient's position was immediately changed to the supine position. A reduction in systolic blood pressure to more than 20% below baseline was treated with an intravenous (iv) fluid bolus. If this was ineffective, 10 mg ephedrine was administrated iv and repeated as needed. Bradycardia, defined as HR ≤45 beats min-1, was treated with atropine 0.5 mg iv as needed.

Following the procedure, the patients were taken to the postanesthesia care unit and observed for 4 hours, after which they were taken to the ward and remained under observation for a total of 24 hours by nurses who were blinded to the protocol.

Pain was assessed with a 10-cm linear visual analog scale (VAS) ranging from 0 (no pain) to 10 (worst pain imaginable) immediately before the spinal injection and 2, 3, and 5 minutes after the injection. Additional VAS scores were obtained every 30 minutes until the end of surgery and 1, 2, 4, 6, 12, and 24 hours postoperatively. The patients who requested additional analgesia or experienced no analgesia within 20 minutes after the administration of spinal anesthesia were considered to have an inadequate block and were excluded from the study.

At the time of each VAS assessment, the patients subjectively rated their experience of nausea and pruritus as none, mild, moderate, or severe. BP, HR, and sensorial and motor blocks were measured. The Bromage scale was used to assess motor block (0=no motor block, 1=inability to raise extended legs, 2=inability to flex knees, 3=inability to flex ankle joints). Maximal block height, 2-segment regression, and regression to S1-2 segments were ascertained using a pinprick at the same intervals as VAS scores.

Patients with a VAS score ≥5 were treated with meperidine 50 mg intramuscularly (im) every 4 hours as needed; no other analgesic and/or sedative agents were permitted during the first 24 hours after surgery. Moderate or severe pruritus was treated with naloxane 40 µg iv in the fentanyl and tramadol groups if requested. Moderate or severe nausea was treated with metoclopramide 10 mg im every 6 hours as needed.

The study data are presented as mean±SD. The groups were compared using Student's t-test and proportions were analyzed using a chi-square test. Normally distributed groups were compared with one-way analysis of variance followed by Dunnett's test. Nonparametric data were compared using the Mann-Whitney rank sum test. P<0.05 was considered statistically significant.

## Results

Although 146 patients were initially enrolled in the study, patients (9 from group S and 1 from group T) were withdrawn because of pain and agitation. The data of 136 patients were used for statistical analysis.

The treatment groups did not differ significantly in terms of patient characteristics or hemodynamic variables (Table 1, 2).

More patients experienced pain in the saline group than in the tramadol HCL or fentanyl group (p<0.05). Four patients in Group S needed im meperidine treatment. More patients in Group F experienced pruritus (p<0.05) but they did not require treatment. More patients in Group T experienced nausea (p<0.05) compared with the other groups. The incidence of bradycardia, decrease in BP greater than 20%, and the use of ephedrine did not differ significantly between groups. The mean respiratory rate or incidence of urinary retention did not differ significantly between the study groups. Oxyhemoglobin saturation was greater than 95% in all of the patients at all times. No postdural puncture headache was reported within the first week after the dural puncture (Table 3).

No significant differences were observed in maximal block height, onset time at the T10 dermatome, start of motor

**Table 3.** Side effects and treatment

| Groups | Fentanyl % | Tramadol HCL % | Saline% |
|---|---|---|---|
| 30%/BP | 15 | 23.07 | 0 |
| 30%/HR | 10 | 8 | 0 |
| Pruritus | 15* | 0 | 0 |
| Nausea | 15 | 30.76* | 0 |
| Pain | 0 | 0 | 26.66* |
| Ephedrine (mg) | 25 | 15 | 10 |

*p<0.05 is statistically significant.

BP: Blood pressure; HCL: Hydrochloride; HR: Heart rate.

**Table 1.** Patient characteristics

| Groups | Fentanyl | Tramadol HCL | Saline | p |
|---|---|---|---|---|
| Age (years) | 56.316±16.85 | 53.154±14.89 | 47.333±18.31 | >0.05 |
| Height (cm) | 172.87±5.61 | 173±9.083 | 170.60±4.879 | >0.05 |
| Weight (kg) | 73.875±10.62 | 82.80±13.08 | 69.231±11.3 | >0.05 |
| Sex (Male/Female) | 42/18 | 24/15 | 27/18 | >0.05 |
| ASA physical status (I/II/III) | 5/9/6 | 3/7/3 | 4/8/3 | >0.05 |
| Duration of surgery (min) | 128±27 | 133±37 | 120±32 | >0.05 |

All values are mean±SD.

P>0.05 is statistically insignificant.

ASA: American Society of Anesthesiologists; HCL: Hydrochloride.

**Table 2.** Hemodynamic parameters

| Groups | Fentanyl | Tramadol HCL | Saline | p |
|---|---|---|---|---|
| Mean BP (mmHg) | 96.85±10.49 | 98.65±12.36 | 91.37±11.11 | >0.05 |
| Heart rate (beats/min) | 77.17±12.27 | 75.92±11.77 | 73.25±7.70 | >0.05 |
| Respiratory rate (rate/min) | 14±3 | 15±3 | 15±2 | >0.05 |
| $SpO_2$ (%) | 98±1.2 | 97±2.2 | 98±2 | >0.05 |

All values are mean±SD.

P>0.05 is statistically insignificant

BP: Blood pressure; HCL: Hydrochloride; RR: Respiratory rate; $SpO_2$: Oxyhemoglobin saturation.

**Table 4.** Postoperative quality of analgesic effects

| Groups | Fentanyl | Tramadol HCL | Saline | p |
|---|---|---|---|---|
| Maximum block height (Thoracic dermatome) | 7.40±1.27 | 8.30±0.75 | 7.66±2 | >0.05 |
| Onset at T10 (min) | 4.80±1.47 | 6.11±2.46 | 5.55±2.40 | >0.05 |
| Beginning of motor block (min) | 5.12±2.95 | 4.92±1.85 | 6.61±3.46 | >0.05 |
| Grade of motor block | 1.95+0.39 | 1.92+0.49 | 2.11+0.60 | >0.05 |
| Two-segment regression of block (min) | 99.25+35.80 | 86.53+24.27 | 107.77+35.01 | >0.05 |
| Regression to S1-2 (min) | 183.75+47.01* | 143.07+14.22 | 149.81+26.78 | <0.05 |

All values are mean±SD.

p>0.05 is statistically insignificant.

HCL: Hydrochloride.

block, or mean time to 2-segment regression in all 3 groups. The mean time to regression to the S1-2 segment was significantly longer in the fentanyl group compared with the tramadol and saline groups (p<0.05) (Table 4).

## Discussion

In this randomized, double-blind, placebo-controlled clinical study our aim was to observe the anesthetic and analgesic effects of intrathecal tramadol compared with intrathecal fentanyl added to bupivacaine with that of a placebo added to bupivacaine in patients undergoing elective transurethral procedures. We found that intrathecal administration of tramadol was not superior to intrathecal administration of fentanyl or placebo.

Few studies have been conducted regarding the intrathecal use of tramadol. The risk/benefit analysis of this technique is controversial.

The basic clinical study we found in a search of the literature about intrathecal tramadol administration was that of Alhashemi and Kaki [15] about the effect of intrathecal tramadol administration on postoperative pain after a transurethral resection of the prostate (TURP). They concluded that intrathecal tramadol was not different from saline in its effect on the postoperative morphine requirement after TURP. We found that in the saline group more patients experienced pain than in the tramadol HCL and fentanyl groups (p<0.05): Four patients in the saline group needed im meperidine treatment.

Singh et al.[10] studied the effects of lumbar-epidural administration of tramadol on lower urinary tract function and found that epidural tramadol increased bladder capacity, compliance, and delayed filling sensations without ill effect on voiding, even for patients with obstructed outflow; however, due to the small number of patients a definite conclusion could not be made. They suggested that these results could guide clinicians to avoid catheterization in cases where epidural tramadol is used for postoperative pain, but that the inhibitory effects of tramadol on electromyography activity need further study. We did not observe any urine retention in our study.

Alici et al.[16] studied the effect of tramadol on the fatty acid composition of rabbit spinal cord and brain and the overall changes in the concentration and number of fatty acids suggested that the spinal drug had the side effect of disrupting the membrane fluidity of the blood-brain barrier, which may cause neurotoxicity. No neurotoxicity was observed in our study.

Chatrath et al.[17] compared the addition of 25 mcg fentanyl and 25 mg tramadol with the administration of levobupivacaine during combined spinal-epidural anesthesia in labor. Adding tramadol to a local anesthetic provided prolonged analgesia with minimal side effects. Fentanyl, when used as adjuvant to a local anesthetic, has a rapid onset of analgesia but may have certain fetomaternal side effects. Frikha et al.[18] compared tramadol and sufentanil used in combined spinal-epidural analgesia in terms of the duration of analgesia and frequency of adverse maternal or fetal effects. A dose of 2.5 mcg intrathecal sufentanil combined with 2.5 mg bupivacaine provided rapid-onset and profound analgesia during the first stage of labor without adverse maternal or fetal effects. Administration of 25 mg intrathecal tramadol with 2.5 mg bupivacaine had longer-lasting analgesia. The major side effect was vomiting Subedi et al.[19] evaluated the effect of intrathecal tramadol on spinal block characteristics and neonatal outcome after an elective caesarean section. Tramadol 10 mg, as an adjunct to bupivacaine for subarachnoid block for caesarean section, showed a longer duration of analgesia with a reduced incidence of shivering compared with intrathecal fentanyl 10 µg.

Afolayan et al.[20] evaluated the effectiveness of intra-operative analgesia produced by intrathecal tramadol and fentanyl during bupivacaine spinal anesthesia for an open appendectomy. They demonstrated that intrathecal tramadol (25 mg) could safely replace intrathecal fentanyl (25 µg) in the management of visceral pain and discomfort during a subarachnoid block for an appendectomy. The pain-free

period, however, was significantly longer in the fentanyl patient group than the tramadol group.

In our study, the onset at the T10 dermatome was fastest in the fentanyl group at 4.80±1.47 minutes, which could be expected based on previous research with opioids as adjuvants to local anesthetics.[12] Onset time was longest in the tramadol group at 6.11±2.46 minutes. The grade of motor block was satisfying in all of the groups. Regression to S1-2 was longest in the fentanyl group at 183.75±47.01 minutes, while it was shortest in the tramadol group at 143.07±14.22 minutes. In the present study, the absence of prolonged motor and sensorial block was most likely due to the low concentration of tramadol (10 mg). It was reported that tramadol administered by intrathecal injection produced a dose-dependent antinociceptive effect in the tail-flick test in 30% of the rats.[12]

Our results indicated that fentanyl added to a local anesthetic provided longer postoperative analgesia compared with tramadol added to the same local anesthetic. We have concluded that tramadol added to a local anesthetic did not demonstrate any significant advantage during spinal anesthesia compared with the other drug combination group studied.

### Disclosures

**Ethics Committee Approval:** Ethics committee of Sisli Hamidiye Etfal Education and Research Hospital 28.05.2005/34.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** There are no conflicts of interests among the authors.

**Funding:** Financial support was provided by departmental sources.

**Authorship contributions:** Concept – S.Ç.; Design – S.Ç., H.Ş.T.; Supervision – S.Ç.; Materials – S.Ç., H.Ş.T.; Data collection &/or processing – S.Ç., H.Ş.T.; Analysis and/or interpretation – S.Ç., H.Ş.T.; Literature search – S.Ç., H.Ş.T.; Writing – S.Ç., H.Ş.T.; Critical review – S.Ç., H.Ş.T.

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