Original Article

Preincisional analgesia with subcutaneous administration of tramadol reduces postoperative pain in patients after open urologic surgeries: A randomized, double-blind, placebo-controlled study

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ABSTRACT

Objective: Blockade of parietal nociceptive afferent nerves by wound infiltration with tramadol may be advantageous in the management of postoperative pain. The purpose of the present study was to assess the efficacy of preincisional subcutaneous administration of two doses of tramadol on postoperative pain relief after open urologic surgeries.

Methodology: Ninety-six patients scheduled for open urologic surgeries were enrolled in this randomized, double-blind, placebo-controlled study. Patients were divided into three groups of 32 subjects each, and they received subcutaneous administrations of tramadol at 1 $mg.kg^{-1}$ (Group T1) or 2 $mg.kg^{-1}$ (Group T2) or subcutaneous administrations of 10 mL of normal saline (Group C) before undergoing the surgeries. Visual analog scale (VAS) scores and analgesic use were monitored for 24 h after the operation.

Results: VAS scores were significantly lower at 15, 30, and 60 min after arrival at the ***post anesthesia care unit*** in Group T2 compared with Group T1 and Group C ($P < 0.05$). Postoperative VAS scores were significantly lower at 4, 8, 16 and 24 h postoperatively in Group T2 compared with Group T1 and Group C. There were no significant differences between Group T1 and Group C on VAS scores at any time point. The time to first rescue analgesia in the postoperative period was significantly lower in Group T2 compared with Group T1 and Group C. The need for postoperative analgesia was significantly lower in Group T2 compared with Group T1 and Group C.

Conclusion: Preincisional subcutaneous administration of tramadol at 2 $mg.kg^{-1}$ provides effective analgesia during the first 24 hour after open urologic surgeries and does not produce significant side effects.

KEY WORDS: Preincisional tramadol, Urologic surgery, Postoperative pain, Subcutaneous infiltration, VAS.

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INTRODUCTION

Optimal postoperative pain management is influenced by the type of surgical procedure performed, surgical approach, duration of the surgery, patient response to the surgery and postsurgical pain, and type of pharmacologic therapy.[1] Accurate management of postoperative pain can be associated with early postoperative discharge. Using adjuvant agents such as local anesthetics, nonsteroidal anti-inflammatory drugs, tramadol, ketamine, steroids,

and nonpharmacological compounds that limit the use of opioids may prevent postoperative adverse effects such as ileus, respiratory depression, nausea, and vomiting. Therefore, these agents can allow more patients to be discharged early from the hospital.[1-3]

Tramadol is a centrally acting analgesic. Its analgesic effects are mediated by weak partial mu opioid receptor agonism, inhibition of 5-hydroxytryptamine (5-HT) and norepinephrine reuptake in the descending inhibitory pathways, and facilitation of 5-HT release.[4,5] Previous studies have shown that tramadol has some local anesthetic properties when it infiltrates the regions surrounding peripheral nerves, without causing significant side effects.[6-8] Robaux et al showed that adding 100 mg of tramadol to 40 mL of 1.5% mepivacaine improves brachial plexus blockade in patients that were candidates for forearm and hand surgeries.[4]

Preemptive administration of analgesic agents prior to incision surgeries is an important approach to optimally preventing postoperative pain.[9,10] Kaki and colleagues[11] showed that local administration of tramadol prior to herniorrhaphy wound closure provides improved postoperative analgesia in comparison to bupivacaine.

To the best of our knowledge, no study has evaluated the analgesic efficacy of preincisional subcutaneous (s.c.) administration of tramadol to the line of incision in patients undergoing urologic surgeries. Therefore, in the present study, we evaluated the analgesic effects of preincisional s.c. administrations of two doses of tramadol (1 $mg.kg^{-1}$ and 2 $mg.kg^{-1}$) compared to saline in patients that underwent open urologic surgeries.

METHODOLOGY

After obtaining approval from our University Ethics Committee, we examined 96 American Society of Anesthesiologists (ASA) physical status I-II patients, aged 18–65 years old, who were scheduled for open urologic surgeries under general anesthesia. All subjects gave written informed consent to participate in this randomized, double-blind, placebo-controlled study. Exclusion criteria included patients with a known history of drug or alcohol abuse in the preceding 6 months, limited communication capacity, tramadol allergy, chronic pain syndrome, renal insufficiency, or hepatic insufficiency. Before the surgery, the patients were informed how to evaluate their pain using a 10-cm visual analog scale (VAS), ranging from 0 (none) to 10 (worst possible pain). Premedication was performed for all patients with 0.05 $mg.kg^{-1}$ intravenous (i.v.) midazolam. After arrival at the operating room, arterial blood pressure [systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and mean arterial pressure (MAP)], heart rate (HR), respiratory rate (RR), and peripheral oxygen saturation (SpO_2) level were monitored noninvasively.

Using random selection of sealed envelopes, the patients were randomized into one of three test groups with 32 patients in each group. Group T1 received 1 $mg.kg^{-1}$ tramadol in 10 mL of 0.9% normal saline locally in the wound, starting from the external oblique aponeurosis up to the skin prior to skin closure. Group T2 received 2 $mg.kg^{-1}$ tramadol in 10 mL of 0.9% normal saline and Group C received 10 mL of 0.9% normal saline using the same administration technique.

An anesthesiologist who did not conduct the drug or saline administrations or the assessment of the postoperative patient responses prepared the syringes for each subject. All administrations were 10 mL in volume. The study drugs were administered by a surgeon who was not involved in the group assignment. The drugs were administered after the induction of anesthesia with 5 $mg.kg^{-1}$ of thiopental sodium and 3 $\mu g.\ kg^{-1}$ fentanyl and administration of 0.6 $mg.kg^{-1}$ atracurium for facilitation of tracheal intubation. All surgical incisions were started 15 min after the administration of tramadol or saline. Maintenance of general anesthesia was performed with 1.2% isoflurane and 50% nitrous oxide in oxygen. Morphine at 1 $mg.kg^{-1}$ was administered for intraoperative analgesia. At the end of the operation, neuromuscular blockade was reversed by i.v. neostigmine at 0.04 $mg.kg^{-1}$ and i.v. atropine at 0.02 $mg.kg^{-1}$. Subsequently, anesthesia was discontinued and the patients were extubated when their airway reflexes returned.

The patients' HR, SpO_2, SAP, DAP, and MAP values were recorded at 15 min intervals during the operation at 15, 30, and 60 min after arrival at the ***postanesthesia care unit*** (PACU) and at 4, 8, 16, and 24 hour postoperatively. After extubation, the patients were transferred to the PACU, where they were observed by an anesthesiologist and a nurse who were unaware of the patient's treatment plan. In the PACU, pain scores were evaluated by the blinded observer physician at arrival and 15, 30, and 60 minutes later using VAS. When patients reaching a modified Aldrete score of greater than 9,[12] they were discharged from the PACU to the ward and the duration of their time in the PACU was recorded.

During the first postoperative day, pain scores were assessed by a physician who was blinded to the treatment assignment at 4, 8, 16, and 24 hour. Moreover, the patients' sedative levels were evaluated using a sedation scale wherein 0 represents awake, 1 represents drowsy but responsive to verbal orders, 2 represents drowsy but responsive to physical stimulus, and 3 represents sleepy but responsive to pain stimulus at 4, 8, 16, and 24 hour. Meperidine at 0.4 $mg.kg^{-1}$ was administered i.v. if the patient's VAS score was more than 4. Furthermore, if the score did not decrease within 10 min, an additional 0.2 $mg.kg^{-1}$ of meperidine was administered. The maximum dose of meperidine administered was 2 $mg.kg^{-1}$ in any 4 hour. The time to first supplementary meperidine administration and the total dose of meperidine administered were recorded.

Complications from the study drug administration, including dizziness, nausea, vomiting, pruritus, and flushing, were recorded in the postoperative period. Metoclopramide at 0.1 $mg.kg^{-1}$ i.v. was administered to patients for vomiting or for nausea lasting more than 10 minutes. The patients classified the pain relief from the analgesia as excellent, good, mild, or weak, and this classification was recorded during the first 24 hour after the operation.

All data were recorded by a physician who was blinded to the treatment assignments. The time from anesthesia induction to the discontinuation of anesthetic drugs, the time from discontinuation of nitrous oxide to extubation, and the time from the first surgical incision to the last skin suture were also recorded. Postoperative evaluation was performed by an investigator who was blinded to the treatment group.

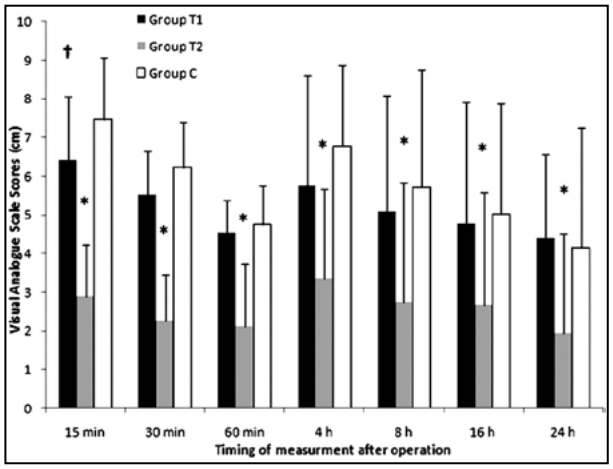

Fig.1: Postoperative visual analog scale scores at 15, 30, and 60 min and 4, 8, 12, and 24 h after the operation. The data are presented as means ± the SD. Group T1 received 1 mg.kg−1 tramadol s.c.; Group T2 received 2 mg.kg−1 tramadol s.c.; Group C received similar volume of normal saline s.c. * P < 0.05 vs. Group T1 and Group C. † P < 0.05 vs. Group C.

The sample sizes were determined based on a power calculation that showed that 32 patients per group were necessary to achieve 80% power to detect a 20% difference in the VAS scoring between Group C and the Groups T1 and T2, with a probability value (P) = 0.05. The data are presented as the mean and standard deviation or as individual numbers. All statistical analyses were performed using the SPSS 16.0 for Windows statistical package. Correlation with sex, ASA physical status, and complication rates was assessed by a Pearson chi-square test or by a Fisher's exact test when appropriate. Differences among the groups were compared using one-way analysis of variance (ANOVA) and post-hoc comparisons at various time points using Bonferroni's type I error rate correction for multiple comparisons. The Kruskal-Wallis test was used to compare nonparametric variables. The Mann-Whitney U test was used to compare pairs of groups. For all statistical tests, $P < 0.05$ was considered statistically significant.

RESULTS

Ninety-six patients completed the study. No patients were excluded from the study. There were no significant differences between the three groups in demographic characteristics, or the duration of anesthesia or the surgery (Table-I). The PACU stay and extubation time were significantly lower in Group T2 compared with Group T1 and Group C ($P < 0.05$) (Table-II). This variable was significantly lower in Group T1 compared with Group C ($P < 0.05$) (Table-II).

VAS scores were significantly lower at 15, 30, and 60 min after arrival at the PACU in Group T2

Table-I: Demographic characteristics, duration of anesthesia, and duration of surgery across the three groups.

Variables	*Group T1 (n = 32)*	*Group T2 (n = 32)*	*Group C (n = 32)*	*P value*
Age (years)	38.5 ± 12.0	37.4 ± 15.4	42.9 ± 15.6	0.273
Weight (kg)	70.5 ± 15.4	69.8 ± 10.7	69.6 ± 12.2	0.945
Sex (M/F)	27/5	24/8	21/11	0.223
ASA (I/II)	20/12	23/9	19/13	0.553
Height (cm)	169.8 ± 7.1	170.2 ± 10.5	167.4 ± 8.8	0.410
Duration of anesthesia (min)	132.8 ± 57.4	133.4 ± 61.3	138.4 ± 61.8	0.158
Duration of surgery (min)	118.1 ± 49.7	117.2 ± 53.9	137.0 ± 52.3	0.233

The data are presented as means ± SD or as individual numbers. Group T1 received 1 mg.kg−1 tramadol s.c.; Group T2 received 2 mg.kg−1 tramadol s.c.; Group C received a similar volume of normal saline s.c.. M/F = male/female.

Table-II: Postoperative analgesic use, time to tracheal extubation, and PACU stay duration across the three groups.

Variable	*Group T1 (n = 32)*	*Group T2 (n = 32)*	*Group C (n = 32)*	*P value*
Time to first analgesic demand (min)	40.0 ± 4.0	172.1± 29.9 *	04.1 ± 1.4	0.000
Postoperative analgesic requirement (mg)	81.9 ± 8.8	48.4 ± 7.8*	83.4 ± 9.0	0.010
Extubation time (min)	16.3 ± 5.5†	12.2 ± 3.9*	21.3 ± 9.2	0.000
Duration of PACU stay (min)	33.9 ± 10.8†	25.7 ± 5.1*	41.5 ± 13.4	0.000

The data are presented as means ± SD. Group T1 received 1 mg.kg−1 tramadol s.c.; Group T2 received 2 mg.kg−1 tramadol s.c.; Group C received a similar volume of normal saline s.c. PACU = Postanesthesia care unit. * P < 0.05 vs. Group TI and Group C. † P < 0.05 vs. Group C.

compared with Group T1 and Group C (P < 0.05) (Fig.1). In Group T1, VAS scores were significantly lower than Group C only at 15 min after arrival at the PACU (P < 0.05) (Fig.1). Postoperative VAS scores were significantly lower at 4, 8, 16 and 24 hour after the operation in Group T2 compared with Group T1 and Group C (P < 0.05). There were no significant differences between Group T1 and Group C in these variables.

There were no significant differences between the three groups in HR, SpO_2, SAP, DAP, and MAP values at the different time intervals throughout the surgery or during the postoperative period. The median sedation levels were not significantly different in three groups at any postoperative period. The time to the first rescue analgesia in the postoperative period was significantly lower in Group T2 compared with Group T1 and Group C (P < 0.05). This variable was not significantly different between Group T1 with Group C.

The postoperative analgesic requirement was significantly lower in Group T2 compared with Group T1 and Group C (P < 0.05). No significant differences between Group T1 and Group C were noted in this regard. The median classification of the pain relief from the analgesia was significantly greater in Group T2 compared with Group T1 and Group C (2.5, 2, 2 respectively, P < 0.05). There were no significant differences between Group T1 and Group C in this regard.

The median nurse satisfaction was significantly greater in Group T2 compared with Group T1 and Group C (4, 2, 1.5 respectively, P < 0.05). This variable was significantly greater in Group T1 compared with Group C. No significant differences were noted in the incidences of adverse effects in the three groups (Table-III). None of the subjects exhibited hypotension (systolic blood pressure less than 90 mm Hg) or bradycardia (heart rate less than 60 beats per min) throughout the surgery or postoperatively.

DISCUSSION

The results of the present study show that preincisional subcutaneous administration of tramadol at 2 $mg.kg^{-1}$ decreased postoperative pain scores significantly compared with s.c. administration of tramadol at 1 $mg.kg^{-1}$ or normal saline solution in patients who underwent open urologic surgeries under general anesthesia. Moreover, this dose of tramadol did not engender any significant side effects. Furthermore, our results confirm that s.c. tramadol at 2 $mg.kg^{-1}$ delays the first request for analgesia and produces a significant meperidine-sparing effect during the first 24 hour after urologic surgeries. In addition, greater patient and nurse satisfaction was noted.

Local anesthetic infiltration of surgical wounds has been found to be effective in many investigations.[7,8,13-15] However, it can be lethal because of central nervous system and cardiovascular toxicity.[16] Some previous studies have shown that tramadol has local anesthetic effects,[4,17] with negligible sedation and adverse cardiovascular effects.[5-8,15] The analgesic and anti-inflammatory effects of tramadol were demonstrated by Grecek et al.[18] Jou and colleagues proposed that tramadol through a similar mechanism to local anesthetics that involves blocking voltage-dependent Na channels.[15] In contrast, Mert et al[19] suggested that calcium facilitates the conduction blocking effects of tramadol but attenuates those of lidocaine.

Guven and colleagues[20] concluded that when tramadol infiltrates the rat sciatic nerve it probably blocks Na channel to a similar degree as lidocaine but more effectively blocks potassium channels

Table-III: Incidence of adverse effects across the three groups.

Variable	*Group T1 (n = 32)*	*Group T2 (n = 32)*	*Group C (n = 32)*
Nausea	0	1	1
Vomiting	1	1	2
Dizziness	1	1	0
Pruritus	1	0	0
Flushing	0	1	1

The data are presented as individual numbers. Group T1 received 1 mg.kg−1 tramadol s.c.; Group T2 received 2 mg.kg−1 tramadol s.c.; Group C received a similar volume of normal saline s.c. There were no significant differences between the three groups.

than lidocaine. They showed that both lidocaine and tramadol extended the depolarization time of the compound action potential (CAP) equally, whereas tramadol lengthened the full width at half maximum of the CAP more than lidocaine because of its potassium channel blocking activity.[20]

In the present study, local wound infiltration with tramadol at 2 $mg.kg^{-1}$ prior to the wound closure in urologic surgeries provided significant postoperative analgesia up to 24 hour in comparison to tramadol at 1 $mg.kg^{-1}$ or saline. Altunkaya and colleagues[7] showed that s.c. administration of tramadol at 2 $mg.kg^{-1}$ had a local anesthetic effect similar to lidocaine at one $mg.kg^{-1}$. They correlated this effect of tramadol to its antinociceptive effect, which could be lengthened into the postoperative period. They found that the duration of analgesia provided by the combined subcutaneous administration of tramadol and adrenaline was significantly longer than that of lidocaine plus adrenaline.

In another study performed by Demiraran et al[8], wound infiltration by tramadol at 2 $mg.kg^{-1}$ provided significant postoperative analgesic effects that were similar to those of 0.25% bupivacaine in pediatric patients who were candidates for herniotomies. The decreased wound pain that was observed 24 hour after preincisional administration of tramadol at 2 $mg.kg^{-1}$, as evidenced by low pain scores and decreased use of analgesics, may be explained by the unusually long duration of tramadol's direct peripheral pharmacologic action or by its preemptive effect on the inflammatory response to the surgery.

The elimination half-life of tramadol as explained by a two-compartment model is 5.01 ± 0.08 h.[21] In two previous studies[22,23] it was shown that parenteral administration of tramadol at the time of wound closure relieved postoperative pain for only 60–90 minutes. In contrast, local administration of tramadol yielded a longer duration of analgesia than the reported elimination half-life of parenteral tramadol. This may be because of tramadol's local effects rather than systemic absorption.

The rationales of preemptive analgesia are, initially, to inhibit or decrease the development of any 'memory' of pain stimulus in the CNS and, consequently, to reduce analgesic need.[24,25] It is probable that tramadol inhibits wind-up in a wide dynamic range of neurons as a consequence of long-lasting C-fiber stimulation.[26,27] The preemptive effect of preincisional administration of tramadol on the inflammatory response to surgery can be explained in the long-lasting effect of tramadol (24 h) on lessening postoperative pain observed in Group T2.

Preemptive treatment with local anesthetics and tramadol have been suggested as methods of preventing transmission of noxious stimuli, stimulation of pain receptors in the spinal cord, and central sensitization.[28,29] The preemptive blockade of the initial nociceptive afferent input to the spinal cord may inhibit the development of long-term changes in the excitability of central neurons and, consequently, prevent both peripheral and central nociceptive processing, which then produces long-lasting antinociceptive effects.[30,31] The analgesic effects of tramadol have been shown to be short-lived when administered after pain stimulation, probably because of a failure to inhibit the maintenance of pain behavior that is mediated by peripheral or central sensitization.[22,23,32] Therefore, it is possible that the prevention of the original neural trigger by local administration of tramadol during the induction of pain may inhibit the maintenance of pain.

The analgesic effects of tramadol could also be explained by synergistic or additive interactions with opioids. One of the mechanisms of severe postoperative pain that leads to the need for progressively higher doses of opioids in postoperative patients is tolerance. It seems that tramadol act specifically to inhibit opioid tolerance and pain sensitization[33], which may shed light on its mechanism of action.

Hopf et al[34] emphasized how postoperative pain affects the inflammatory response and increases the release of catecholamines as this leads to decreased wound perfusion and oxygenation. It can be concluded that wound infiltration with tramadol may provide pain control with the added benefits of increasing wound perfusion and oxygenation, and this may facilitate wound healing.

In the present study, there were no significant differences between the three study groups in the incidence of adverse effects. These effects may depend on the dose, the route of administration, and the timing of wound infiltration.

The present study has some limitations. We only recorded the total consumption of meperidine on first day after the surgeries. Consequently, our results cannot show whether the meperidine sparing effect of tramadol was prolonged beyond this time frame. Another limitation of the study was that we did not administer tramadol again during the postoperative period. Therefore, the effects of continuing the medication could not be evaluated.

In conclusion, preincisional s.c. administration of tramadol at 2 $mg.kg^{-1}$ provides effective anal-

gesia during the first 24 hour after open urologic surgeries without significant side effects. As, to the best of our knowledge, no study has evaluated the pharmacokinetics of locally infiltrated tramadol, this should be investigated in future studies. Nevertheless, our results are interesting in light of their potential clinical application to the other types of surgeries.

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Authors Contribution:

MRS, AH, and FG planned and finalized the study. MRS and AH conducted the statistical analyses and prepared the first version of article. All authors read and approved the article.