Original Article

Preemptive subcutaneous tramadol for post-operative pain in lower abdomen surgeries: A randomized double blinded placebo-control study

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Abstract

Background: Recently, the preemptive analgesic effects of subcutaneous infiltration of tramadol (T) in the site of incision have not been extensively studied. In this study, we investigated the effect of subcutaneous T infiltration before the incision of surgery on post-operative pain, in lower abdomen surgeries.

Materials and Methods: This double-blind study was carried out on 90 patients (18-65 years) of American Society Anesthesiologists physical status I and II who were candidates for a lower abdomen surgery during 2011. They were randomly assigned to receive preemptive subcutaneous T or normal saline (NS). The visual analogue scale for pain (VAS) in rest and cough position and opium total dose consumption were compared between two groups in times 0, 15, 30, 60 min and 2, 4, 6, 12, 24 h after the surgery.

Results: The VAS in cough and rest position in the first 24 h following the surgery was lower in group T ($P < 0.05$). Opium consumption was lower in group T ($P < 0.05$).

Conclusion: Subcutaneous preemptive infiltration of T before surgical incision reduces post-operative opioid consumption.

Key Words: Analgesia, pain, post-operative, preemptive, subcutaneous, tramadol

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INTRODUCTION

Pain is an important impediment to recovery from surgery and anesthesia in the post-operative period.[1] Opioids are the most effective forms of medicine that are used in relieving pain, therefore, a general goal in old patients is to minimize exposure to the side effects of prolonged, relatively systemic narcotics while providing adequate analgesia.[2,3] So, wound infiltration with local anesthetics has been the preferred analgesic method since the early 20th century.[4] Tramadol (T) is a central analgesic with a dual mechanism of effect.[5,6] It causes the activation of opioid and non-opioid systems which are involved in the inhibition of pain. The effect of non-opioid component of Tis mediated through $\alpha_2$agonistic and serotonergic activities.[7,8] As a week opioid, Tramadol (T) also is a centrally acting analgesic selective for μ-receptors with local anesthetic actions on peripheral nerves.[9] Some attempts have been made until now to reduce post-operative pain through incisional infiltration. For example,

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subcutaneous wound infiltration with T reduced post-operative opioid consumption and produced less nausea and vomiting than dose intravenous (IV) administration after pyelolithotomy.[10] Another study could not identify any significant difference in VAS and morphine consumption following T administration.[11]

The degree of post-operative pain is multifactorial and depends on variables such as type and duration of operation, type of anesthesia used, and patient's mental and emotional status.[12] Also, the post-operative analgesic effects of preemptive subcutaneous infiltration of Tin the site of surgical incision have not been extensively studied based on the location of incision and surgery. In addition, lower abdominal surgeries are common operations in many countries. So, the aim of our study was to evaluate the effects and complications of preemptive subcutaneous T infiltration in comparison with a control group in lower abdominal surgeries.

MATERIALS AND METHODS

After obtaining institutional approval from the ethics committee of Isfahan University of Medical Sciences, this double-blind randomized clinical trial was carried out in the AL-Zahra general hospital, Isfahan, Iran during 2011. Ninety healthy American Anesthesiologists' Society (ASA) physical status I and II, 18-65-year-old patients scheduled for elective lower abdomen surgeries were entered in the study. Written informed consent was obtained from all the patients after full explanation of the goals and procedures of the study.

Patients with a history of acute or chronic pain, alcohol or drug abuse, past lower abdomen surgery, and morbid obesity were not included. Moreover, any patient with a history of intolerance or adverse reactions, or showing anaphylactic reactions to the medications used in the study was excluded. Patients who endured post-operative bleeding or needed blood transfusion were excluded too. Informed consent was obtained from the patients. Before anesthesia induction, patients were randomized using computer-generated random numbers and received either preemptive subcutaneous T (group T) or normal saline (NS) (group NS). All patients were instructed pre-operatively about the use of VAS (0 = no pain to 10 = most pain imaginable). The preparation of study drugs was performed by an anesthesiologist who was not involved in the data collection. All patients were pre-medicated with a tablet of clonazepam1 mg and 150 ml water 2 h before surgery. Fluid therapy was the same in the groups based on 4,2,1 rule using 1/3 dexrtose water-2/3 NS solution before surgery.

After arrival to the operating room, patients were monitored by an electrocardiogram (ECG), noninvasive blood pressure measurement and pulse oximetry throughout the study. Then, anesthesia was induced with fentanyl 2 μg/kg, sodium thiopental 5 mg/kg and atracurium0.5 mg/kg IV, and intubation was performed with cuffed tube number 7.5-8. Then, group T patients received 2 mg/kg T (attenuated with N/S to the volume of 20 cc) subcutaneously before incision at the site of surgical incision. Group NS patients received 20 cc N/S (placebo), respectively. Injections were performed by the surgeon. The syringes were all unlabeled and the anesthesiologist and the surgeon were blinded to the patients' treatment assignments. Then anesthesia was maintained with oxygen 50%, nitrous oxide 50% and 0.8-1.2% isoflorane to maintain the blood pressure and pulse rate within 20% of the patient's baseline values. Tidal volume was 10 cc/kg and End Tidal (ET) carbon dioxide (CO_2) was maintained within 35-45. No additional narcotic was given in the operating room. At the end of the surgery, neuromuscular blockade was reversed with neostigmine 2.5 mg IV and atropine 1.25 mg. After extubation, patients were transferred to the recovery room and were tended by nurses who were also blinded to the patients' treatment assignment.

VAS scores were recorded 0, 15, 30, 60 min and 2, 4, 6, 12, 24 h post-operatively after the patients' admission into the recovery room. These scores were obtained at rest and cough position. In addition, heart rate (HR), respiratory rate (RR), mean arterial pressure (MAP) and sedation score (SS: 1. alert, 2. Occasionally drowsy, 3. frequently drowsy, 4. sleepy or easy to arouse, 5. somnolent or difficult to arouse) were recorded in these times, respectively. Each time a patient had VAS score ≥4, he received 0.05 mg/kg morphine to maintain VAS score <4. For each time of nausea and vomiting, a patient received 0.15 mg/kg metoclopramide IV. Total dose of opium and metoclopramide consumption in 24 h following the surgery, first opium requirement time and post-operative complications (including dizziness, nausea, vomiting, headache and seizure) were also recorded. Satisfaction status of patients (scaled by five different degrees including: Outstanding, very good, good, fair, and bad) was also recorded within 24 h following the surgery. Anesthesia time was considered as the time between induction of anesthesia and patient's extubation. Operation time was defined as the time between skin incision until the latest suture. Extubation time was described as the time between the discontinuation of anesthetics and extubation. Recovery time was based on the time between extubation and discharge from recovery room using modified Alderet score.

Based on a pilot study, the difference between the mean VAS of two groups was calculated (0.8) and according to the findings, the recurred sample size for each group was calculated to be 45(a = 0.05, b = 0.2). We used independent sample *t*-test for quantitative variables and χ^2 test for qualitative variables in SPSS software V.17 (Chicago, IL, USA).

RESULTS

All patients completed the study [Figure 1]. The 90 patients enrolled in the study were divided into two groups. There were no significant differences in the demographic data of the patients [Table 1].

The nausea average in 24 h following the operation was higher in group T ($P < 0.05$).

Patients who received T had less morphine consumption and average time for the first opium requirement was longer in them; however, they had more metoclopramide consumption in comparison to the control group [Table 2].

The VAS score was recorded to be lower in group T in 24 h after operation, and there were no statistic differences in the other times between the groups.

MAP and HR were measured in different times during and following the operation [Table 3]. The differences were not statistically significant in these parameters between the groups.

Also, any difference about RR and sedation scores in all the times between two groups has not been found.

Figure 2 shows the overall satisfaction status in both groups. It was reported to be higher in patients who received T ($P < 0.001$ using Chi-square test).

According to our findings nausea ($P = 0.017$), vomiting ($P = 0.038$) and headache ($P = 0.04$) were more frequent in group T.

DISCUSSION

There still much controversy regarding the concept of preemptive analgesia.[13,14] Preemptive analgesia is an analgesic regimen initiated before the onset

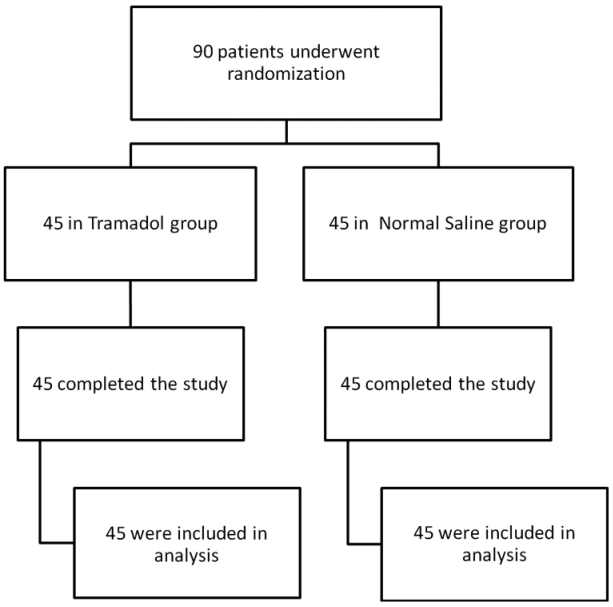

Figure 1: Flow diagram of enrolled study patients

Table 1: Baseline and surgical characteristics[a] among the groups

Characteristic	Tramadol *N*=45	Placebo *N*=45	*P* value
Age (year)	46.9±13.99	45.1±16.3	0.67
Sex (male/female)	26/19	22/23	0.58
Height (cm)	170±9.3	169±8	0.83
Weight (kg)	70.4±11.5	65.6±10.8	0.14
Operation time (min)	125±84.9	147±98.3	0.4[b]
Anesthesia time (min)	132.4±80.9	160.2±99.5	0.28[b]
Extubation time (min)	11.4±8.3	12.4±9.8	0.7[b]
Recovery time (min)	40±16.7	44±16	0.39[b]
Nausea (%)	92	60	0.017[b]
Vomiting (%)	56	42	0.038[b]
Metoclopramide dose (mg)	8±8.6	3.2±5.56	0.02[b]

[a]Mean±SD; [b]independent sample *t*-test

Table 2: VAS score in rest and cough at 0,15, 30, 60 min and 2, 4, 6, 12, 24 h following the operation

Parameter	Tramadol *N*=45	Placebo *N*=45	*P* value[a]
VAS, rest			
0 min	2±1.35	1.88±1.53	0.77
15 min	2.4±0.86	2.28±1.24	0.69
30 min	2.56±1	2.6±0.81	0.87
60 min	2.52±0.96	3.04±1.39	0.13
2 h	2.44±1.19	2.52±1.04	0.80
4 h	2.56±1.44	2.96±1.56	0.35
6 h	2.4±1.52	2.90±1.20	0.15
12 h	1.92±0.9	2±0.81	0.74
24 h	1.56±1.29	2.6±1.31	0.004
VAS, cough			
0 min	3.6±1.38	3.7±1.48	0.84
15 min	3.8±1.15	4.12±1.23	0.34
30 min	3.8±1.22	4±1.35	0.58
60 min	4.2±1.25	4.44±1.12	0.48
2 h	3.6±0.7	4±1.44	0.21
4 h	3.6±1.19	3.64±0.9	0.89
6 h	3.24±0.87	3.48±1.12	0.4
12 h	3.36±1	3.68±1.21	0.32
24 h	2.88±1.12	4±1.45	0.003
Analgesic time (min)	247±199.9	126.7±149.7	0.02
Morphine dose (mg)	5.1±5	8.6±4.8	0.013

VAS: Visual analog scale; [a]independent sample *t*-test

Table 3: MAP and HR at 0, 15, 30, 60 min and 2, 4, 6, 12, 24 h following the operation

Parameter	Tramadol *N*=45	Placebo *N*=45	*P* value[a]
MAP (mmHg)			
0 min	92.3±8.4	93.1±9.2	0.32
15 min	91.5±7.8	92.8±6.5	0.52
30 min	91.9±4.8	90.9±7.9	0.99
60 min	93.3±6.4	96.2±6.51	0.12
2 h	94.7±5.7	96.3±5.9	0.33
4 h	94.2±5	94.7±5.8	0.73
6 h	94.1±6.4	94.7±5.8	0.77
12 h	92±5.3	92.2±6.9	0.88
24 h	91.9±5.6	93.1±7.8	0.53
HR (beat/min)			
0 min	101.9±9.2	94.48±17.1	0 min
15 min	100.1±10.4	93.2±14.9	15 min
30 min	96.4±10.7	92.3±14.7	30 min
60 min	86.2±11.3	91±12.5	60 min
2 h	86.1±11.4	90.3±12.05	2 h
4 h	83.4±8.6	85.2±8.7	4 h
6 h	80.7±6.9	81.7±7.5	6 h
12 h	80.9±6.3	84.1±7.6	12 h
24 h	83.7±5.8	85.4±8.7	24 h

MAP: Mean arterial pressure; HR: Heart rate; [a]independent sample *t*-test

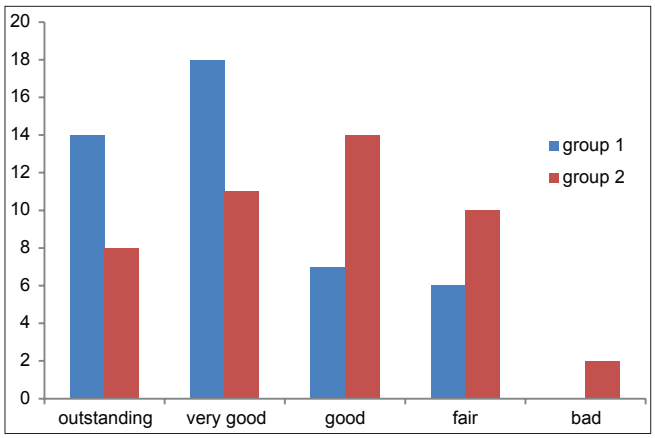

Figure 2: The overall satisfaction status in both groups

of tissue trauma. It is based on the theory of prevention of central pain sensitization. This concept was described first by Crile.[15] Opioids have long been the mainstay for post-operative pain relief.[16] Many studies have shown that the peripheral local anesthetic effects of T are related to those of Codein.[9,17,18]

The aim of our study was to evaluate the analgesic efficacy of preemptive T in treating pain after elective lower abdomen surgeries. We demonstrated that preemptive analgesia given by pre-incisional infiltration with T2 mg/kg subcutaneously, has a significant and beneficial effect on post-operative pain in the first 24 h following the operation and reduces post-operative opioid consumption in lower abdominal surgeries.

Khajavy *et al*. found that subcutaneous wound infiltration with T following pyelolithotomy reduces post-operative opioid consumption compared to IV administration.[10] Ozyilmaz *et al*. showed that wound infiltration with combined levobupivacaine and T resulted in elimination of post-operative analgesic demand and reduction in the incidence of side effects compared with levobupivacaine or Talone.[19] In another study, Isiodria-Espinoza *et al*. have demonstrated that administration of submucous local T after impacted mandibular third molar surgery reduced analgesic consumption in comparison to placebo.[20] In another study by Unlugene *et al*. a considerable decrease in opium consumption following T administration after major abdomen surgeries has been noted.[21] Altunkaya *et al*. demonstrated that the duration of post-operative analgesia provided by subcutaneous wound infiltration with T was longer in comparison with those who received lidocaine.[9]

Contrary to our findings, there are other studies that could not identify any significant difference in VAS or opium consumption following T administration.[11] Santos *et al*. concluded that a difference between IV and subcutaneous T regarding the quality of analgesia was not observed during the 8 h following its administration. They compared subcutaneous and IVT 1.5 mg/kg, diluted in 100 mL of NS and administered over 5-10 min at the end of the surgical procedure (skin closure).[22] A study by Hassan *et al*. showed that butorphanol 1 mg was more effective than T 50 mg in respect to post-operative analgesia in mandibular third molar surgery.[23] Another study by deCosta Arajua *et al*. has noted that nimesulide and T chlorhydrate demonstrate similar preemptive analgesic effects when used in lower third molar surgeries.[24]

We did not find any statistic difference in operation time, general anesthesia time, extubation time and recovery time between the groups, and there was no significant difference in MAP, HR, RR and SS between two groups but a significant change in total morphine consumption was noted between them. Patients who received T had less opioid consumption and the time of the first opioid requirement was longer in them.

Total dose of metoclopramide consumption and frequency of nausea and vomiting were also higher in the group who received T. Considering that the main adverse effects of Tare nausea and vomiting,[25,26] it could be due to the systemic absorption of T after infiltration. The variable incidence of nausea and vomiting associated with T reported in the

literature seems to be related to the administration route and doses used.[22]Altunkaya *et al*. used 2 mg/kg of T and only one out of 20 patients developed nausea and prolonged analgesia, over 24 h of evaluation in the post-operative period of lipoma excision.[9] The absence of statistically significant differences regarding the incidence of nausea and vomiting when using IV and subcutaneous T has been demonstrated.[22] In spite of that, Khajavy *et al*. found that subcutaneous T wound infiltration produces less nausea and vomiting than does IV administration.[10]

It is also notable that the frequency of headache (another adverse effect of T) was higher in those who received T; however, all of these patients reported their headache to be mild to moderate and treated successfully with oral NSAIDs. Another study demonstrated skin rash due to histamine release after T injection,[27] however, such a complication was absent in our study.

In spite of the fact that some of the patients in group T experienced adverse effects of T, there was a statistically significant difference in patients' satisfaction between the groups. It shows that post-operative pain control is an important aspect in pre-operation patient care. Our findings were similar to results of several studies which have noted that use of analgesic agents such as T during the surgery, reduces the patients post-operative pain and post-operative need for opioids.

We didn't measure the serum concentrations of T and it's correlation to analgesic effect in different times.

CONCLUSION

In conclusion considering the mentioned studies, preemptive subcutaneous infiltration of T, is not only an appropriate pain relieving method for post-operative pain treatment and reduces the need for more opioid considerably but also increases patient's satisfaction following the surgery. Yet, further studies should be planned in this regard.

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