TÜBİTAK

Original Article

Turk J Med Sci
2012; 42 (3): 395-401
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E-mail: medsci@tubitak.gov.tr
doi:10.3906/sag-1103-53

Epidural tramadol infiltration decreases postoperative analgesic consumption after lumbar microdiscectomy

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Aim: To investigate the postoperative analgesic effects of epidural tramadol infiltration. Tramadol is a weak opioid that has local anesthetic and antiinflammatory properties.

Materials and methods: Sixty patients of American Society of Anesthesiologists class I or II undergoing lumbar microdiscectomy with general anesthesia were included in the study. The induction of anesthesia was performed with propofol (2-2.5 mg kg^{-1}), rocuronium bromide (0.5 mg kg^{-1}), and fentanyl (1 µg kg^{-1}). A sevoflurane and N_2O/O_2 (FiO_2 = 35%) mixture was used for maintenance. Patients were randomly divided into 2 groups. Tramadol (1 mg kg^{-1}) in a 5-mL saline epidural infiltration was given in the study group at the end of the operation, before surgical closure, and saline in the same volume was given to the control group. Pain was assessed by a visual analog scale (0 to 10 cm) at 4-h intervals during the first postoperative 24 h. A patient-controlled analgesia (PCA) device was adjusted to deliver fentanyl (15 µg bolus) on demand, with a 10-min lockout interval.

Results: No significant difference was found in the visual analog scales between the groups. Tramadol infiltration significantly decreased fentanyl consumption in the first 24 h (fentanyl dose in the control group: 328.5 ± 221.8 µg, tramadol group: 194.5 ± 147.4 µg, P = 0.030). The number of demands for PCA were 51.2 ± 77.9 and 20.1 ± 23.7 in the control and the tramadol groups, respectively (P = 0.02). No difference was found in side-effect profiles between the groups.

Conclusion: Tramadol administration to the epidural space significantly decreased analgesic consumption in patients undergoing microdiscectomy.

Key words: Analgesia, postoperative, tramadol, epidural infiltration

Lomber mikrodiskektomi operasyonundan sonra epidural tramadol infiltrasyonu postoperative analjezik gereksinimini azaltır

Amaç: Çalışmanın amacı epidural tramadol infiltrasyonunun postoperatif analjezik etkilerini araştırmak. Tramadol lokal anestezik ve antienflamatuvar özellikleri de bilinen zayıf opioiddir.

Yöntem ve gereç: Genel anestezi altında lomber mikrodiskektomi operasyonu geçiren ASA I veya II sınıfı 60 hasta çalışmaya alındı. Anestezi indüksiyonu 2-2.5 mg kg^{-1} propofol, 0.5 mg kg^{-1} roküronyum bromid, ve 1 µg kg^{-1}fentanil ile sağlandı. Anestezi idamesinde % 2-2,5 sevofluran ve N_2O/O_2 (FiO_2 = % 35) karışımı kullanıldı. Hastalar rastgele iki gruba ayrıldı. Çalışma grubunda operasyonun sonunda cerrahi saha kapanmadan önce epidural bölgeye 5 mL salin içinde 1 mg kg^{-1} tramadol verilirken, kontrol grubunda hastalara eşit volümde salin uygulandı. Ağrı vizüel analog skala (VAS) ile (0 ila 10 cm) her 4 saatte bir postoperatif ilk 24 saat boyunca değerlendirildi. Hasta kontrollü analjezi (HKA) cihazı 15 µg fentanil bolus istek 10 dakika kilitli kalacak şekilde ayarlandı.

Bulgular: Her iki grup arasında VAS değerleri açısından fark yoktu. Postoperatif ilk 24 saat fentanil tüketimi kontrol grubunda 328,5 ± 221,8 µg ve tramadol grubunda 194,5 ± 147,4 µg bulundu (P = 0,030). HKA bolus istek gereksinimi

Received: 25.03.2011 – Accepted: 06.07.2011

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ise kontrol grubunda 51,2 ± 77,9 ve tramadol grubunda 20,1 ± 23,7 tespit edildi (P = 0,02). Yan etki profilleri arasında fark bulunmadı.

Sonuç: Mikrodiskektomi operasyonu geçiren hastalarda epidural bölgeye uygulanan tramadol infiltrasyonu analjezik gereksinimi belirgin ölçüde azaltmaktadır.

Anahtar sözcükler: Analjezi, postoperatif, tramadol, epidural infiltrasyon

Introduction

Tramadol hydrochloride is a synthetic codeine analog that has opioid and nonopioid properties (1). It decreases pain in the spinal cord with a weak affinity to the μ-opioid receptors by inhibiting noradrenaline and serotonin reuptake. The side-effect profile is milder when compared with the strong opioids, and tramadol can be administered via oral, intramuscular, intravenous, and epidural routes. Tramadol has been widely implemented for the relief of postoperative pain and the epidural route has been proven safe according to large-scale studies performed using the caudal or epidural route (2,3).

The local anesthetic effect of tramadol was investigated and compared with that of lidocaine for minor surgery, and it was found to be an efficient alternative to lidocaine (4). Akkaya et al. (5) reported that, compared to intravenous administration, peritonsillar tramadol infiltration at a dose of 2 mg kg^{-1} significantly decreased analgesic requirements and postoperative nausea and vomiting through its local anesthetic or antiinflammatory effects. Experimental studies also support its antiinflammatory and local anesthetic properties (6-8).

In a previous study, a peripheral model of inflammatory hyperalgesia was demonstrated to induce proinflammatory cytokines in the spinal fluid. Although tramadol is thought to act via a different mechanism for alleviating inflammatory pain, it decreased the concentration of proinflammatory cytokines in the spinal cord of rats, as with paracetamol (9). Preemptive intraarticular tramadol has also been demonstrated to decrease the inflammatory pain threshold in an animal model (10). These results indicate the beneficial effects of tramadol infiltration in a lumbar model of surgical inflammation and pain.

The present study aimed to determine the postoperative analgesic effects of epidural tramadol infiltration at 1 mg kg^{-1} before surgical closure in patients undergoing lumbar microdiscectomy.

Materials and methods

Sixty patients of American Society of Anesthesiologists (ASA) physical status I or II were included in the study after obtaining approval from the local ethics committee (No: 2008-099). Patients were informed of how to use the patient-controlled analgesia (PCA) device and the visual analog scale (VAS) during the preoperative visit. Patients with severe comorbidities including ASA physical status of III or higher, chronic analgesic consumption, analgesic intake within 24 h, or history of allergy to the study medications were excluded from the study.

Patients were randomly assigned to 2 groups using sealed envelopes that were selected by patients before the operation. Electrocardiogram (ECG) at derivation II, noninvasive arterial blood pressure, oxygen saturation, end tidal CO_2, and temperature (Datex-Ohmeda, Cardiocap 5 Monitor, Helsinki, Finland) were monitored and measurements were recorded every 5 min. Venous access was achieved on the nondominant hand with a 20-G cannula. Induction of anesthesia was performed using propofol at 2-2.5 mg kg^{-1}, rocuronium bromide at 0.6 mg kg^{-1}, and fentanyl at 1 μg kg^{-1}. Sevoflurane (end tidal concentration: 2%-2.5%) in an oxygen-N_2O mixture (FiO_2 = 35%) was adjusted for maintenance after endotracheal intubation. The tidal volume was set at 8-10 mL kg^{-1} and respiratory frequency was adjusted according to the end tidal CO_2 value, which was maintained at between 4.5 and 5.5 kPa (Julian model, Dräger, Lübeck, Germany). Tramadol at 1 mg kg^{-1} in saline (5 mL) in Group T or an equal volume of saline in the control (Group C) was injected into the epidural space before the surgical closure. The study drugs were freshly prepared in a different room by one of the investigators (AA) not involved in any of the further evaluations. An atropine (10 μg kg^{-1}) and neostigmine (30 μg kg^{-1}) mixture was administered for antagonizing residual neuromuscular block. After the patients were admitted to the recovery area, the

PCA devices (Abbott Laboratories, North Chicago, IL, USA) were attached when required. Fentanyl (15 μg) was adjusted for a bolus dose with a 10-min lockout interval. Postoperative pain was assessed with a VAS using a 10-cm plastic scale ranging between 0 (no pain) and 10 (worst imaginable pain). Patients were instructed to define their pain by the scale every 4 h during the first postoperative 24 h. The fentanyl bolus dose was increased to 20 μg in the case of moderate to severe pain, when the VAS value was over 7. An 8-mg infusion of lornoxicam (Xefo, Nycomed GmbH, Vienna, Austria) was administered as a rescue analgesic when there was no change in pain. Patients were eligible for transfer to the surgical ward when full cooperation was present with no hemodynamic instability for at least 30 min and they were able to move their extremities. The side-effect profile in the first postoperative 24 h was also recorded.

Statistical analysis was performed using SPSS 15.0 (SPSS Inc, Chicago, IL, USA). Our preliminary results indicated that a minimum of 24 patients for each group were required in order to determine a 35% difference in analgesic consumption at any observation period with a power of 0.8. The number of patients was accepted as 30 for possible dropouts and to increase the power. Multiple comparisons were performed using repeated measures of ANOVA. Categorical data such as sex and ASA physical status were evaluated with a chi-square test, and parametric values including demographic variables, hemodynamic changes, and analgesic consumption were assessed with an unpaired Student's t-test. Nonparametric data such as VAS scales were compared with Kruskal-Wallis analyses. $P < 0.05$ was considered statistically significant.

Results

All of the patients were able to complete the study; therefore, the data of 60 patients were analyzed. Demographic characteristics of the study groups and operation and anesthesia periods are shown in Table 1. There was no significant difference between patients in terms of age, weight, height, sex, ASA physical status, and the durations of operation and anesthesia ($P > 0.05$), with the exception of body mass index (BMI), which was significantly increased in Group T ($P = 0.012$).

Hemodynamic variations of the study groups during the operation and in the early postoperative period were also similar, and the patients did not require medication during the course of the observation periods (Figures 1A and 1B).

Differences in the VAS values in the study groups in the first postoperative day are demonstrated in Figure 2. There was no significant change in the VAS values during the 24-h observation period. The cumulative PCA demand and fentanyl consumption in the first postoperative 24 h are shown in Figures 3 and 4. Time-related PCA demands were significantly lower in Group T when compared with Group C (0 h, $P = 0.022$; 4 h, $P = 0.012$; 8 h, $P = 0.013$; 12 h, $P = 0.020$; 16 h, $P = 0.020$; 20 h, $P = 0.022$; and 24 h, P =

Table 1. Patient demographics and duration of operation and anesthesia (values are given as mean ± SD).

	Group T n = 30	Group C n = 30	P-value
Age (years)	50.3 ± 12.6	51.3 ± 9.3	0.836
Height (cm)	166.2 ± 6.9	167.5 ± 8.1	0.682
Weight (kg)	79.9 ± 11.3	72.6 ± 13.1	0.08
BMI (kg/m^2)	28.37 ± 4.14	25.82 ± 3.39	0.012
Sex (F/M)	18/12	16/14	0.602
ASA (I/II)	14/16	17/13	0.438
Operation time (min)	126.1 ± 57.5	112.0 ± 37.3	0.321
Period of anesthesia (min)	139.3 ± 59.7	126.6 ± 36.6	0.385
Period of stay in PACU (min)	39.7 ± 13.2	43.8 ± 15.4	0.267

PACU: Postanesthesia care unit.

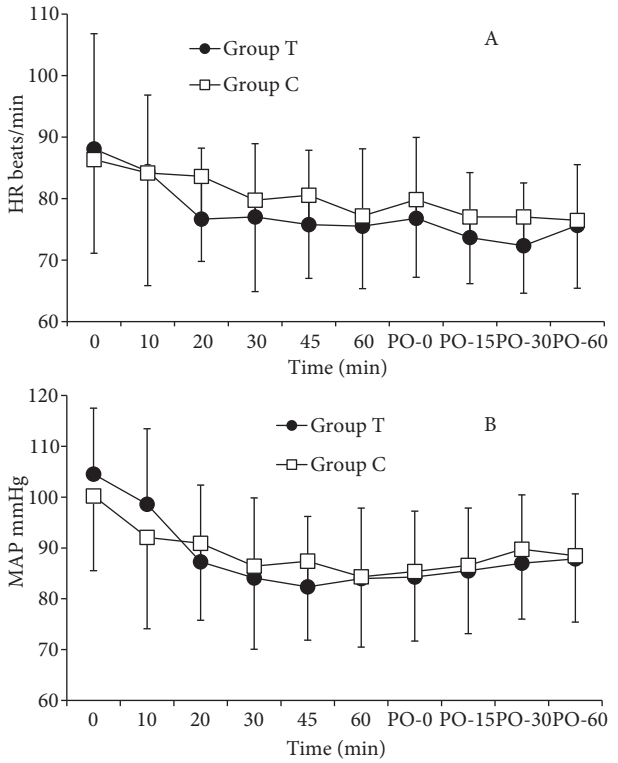

Figure 1. A) Heart rate (HR) and B) mean arterial blood pressure (MAP) changes in the study groups, *P < 0.05.

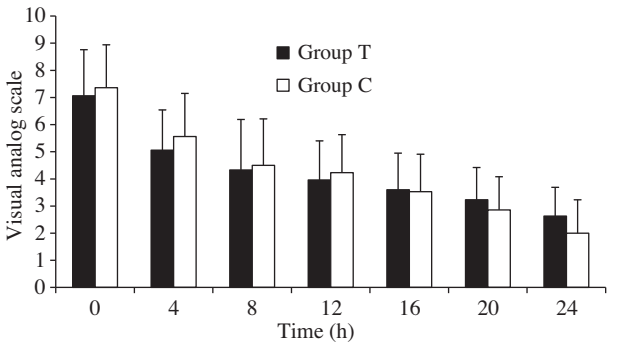

Figure 2. Distribution of visual analog scales.

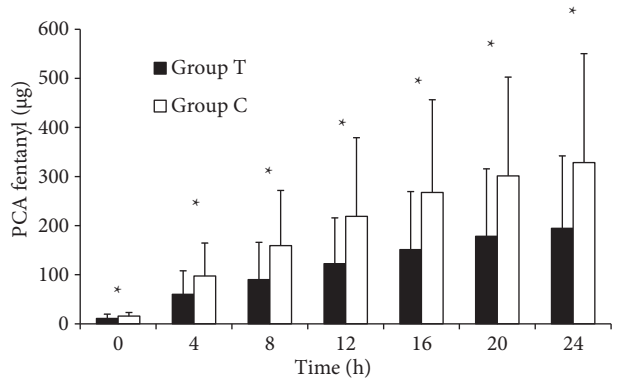

Figure 3. Cumulative PCA fentanyl consumption, *P < 0.05 vs. control group.

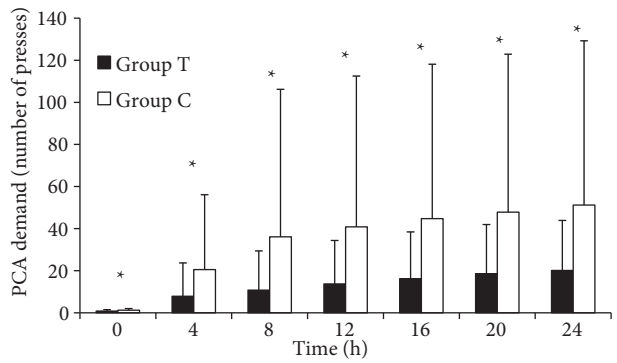

Figure 4. Time-related PCA fentanyl demands, *P < 0.05 vs. control group.

0.030). Patients did not require a dose adjustment or rescue analgesic administration. Cumulative opioid consumption was also found to be significantly lower in Group T at all of the observation periods (0 h, P = 0.022; 4 h, P = 0.016; 8 h, P = 0.010; 12 h, P = 0.024; 16 h, P = 0.011; 20 h, P = 0.017; and 24 h, P = 0.018). Fentanyl consumption in the first 24 h was 194.5 ± 147.4 µg in Group T and 328.5 ± 221.8 µg in Group C (P = 0.030). The total number of PCA demands in the first 24 h was 20.1 ± 23.7 in Group T and 51.2 ± 77.9 in Group C (P = 0.02). Time-related changes in opioid consumption and demands were also significant for Group T (Mauchly's sphericity test, P < 0.001 for both groups) when multiple comparisons were performed.

The distribution of the side-effect profile of the 2 groups is depicted in Table 2. None of the patients indicated numbness, paresthesia, or motor weakness during the postoperative period. There was no statistically significant difference between the groups in the side-effect profile.

Discussion

Epidural tramadol infiltration immediately before the surgical closure significantly decreased opioid consumption and PCA requirements in patients undergoing lumbar microdiscectomy. There was

Table 2. The distribution of the side effects, N (%).

	Group T n = 30	Group C n = 30	P-value
Nausea	14 (46.6%)	10 (33.3%)	0.292
Vomiting	8 (26.6%)	5 (16.6%)	0.347
Dizziness	1 (3.3%)	2 (86.6%)	0.513
Headache	6 (20%)	5 (16.6%)	0.739

no significant difference between the groups with respect to the VAS value or side-effect profile. It was surprising to see the decrease in the cumulative opioid consumption according to the elimination half-life (5-6 h) of the drug (11).

There are few studies concerning the effects of epidural tramadol administration for postoperative analgesia. When compared with other opioids, a lower incidence of side effects was reported, including ventilatory parameters that seem to be better preserved with epidural tramadol. A preemptive caudal epidural tramadol and bupivacaine mixture significantly decreased pain scores and increased the period before the first analgesic requirement in lumbosacral spine surgery (12). However, the sole effect of tramadol is unpredictable due to its combination with a long-acting local anesthetic. The analgesic effects of epidural morphine (4 mg) or tramadol (100 mg) were found to be equal, but a lower incidence of respiratory depression was observed with tramadol in patients undergoing lower abdominal surgery (13). The effect of epidural tramadol was determined to last 9.6 h, and it seldom required supplemental analgesia but it increased the incidence of nausea and vomiting by about 50% (14). In order to alleviate postoperative nausea and vomiting, the addition of droperidol to the tramadol decreased the onset and increased the duration of analgesia in a study on patients undergoing lower abdominal surgery (15). Turker et al. (16) compared repeated doses of epidural tramadol with morphine in patients undergoing thoracotomy and demonstrated that tramadol treatment was associated with a lower incidence of sedation and less influence on the oxygenation. In a study comparing the analgesic effects of single-dose epidural tramadol with morphine in pediatric patients undergoing urologic surgery, the incidence of sedation and respiratory depression along with allergic rash and itching were increased in the morphine group (17). In major urologic surgery, a tramadol-bupivacaine combination administered with an epidural PCA produced intense analgesia with a lower incidence of side effects when compared with bupivacaine or tramadol alone (18). The influence of tramadol on antinociception may result in decreased primary sensitization at the surgical site, which constitutes the main difference in this study.

Caudal epidural tramadol administration has been largely investigated in pediatric patients. Preemptive caudal tramadol at 2 mg kg^{-1} was equally as efficient as morphine at a dose of 0.03 mg kg^{-1} (19). Although caudal tramadol administration was considered to be as safe and efficient as bupivacaine, the analgesic period was not prolonged when the 2 drugs were combined (20,21). The common side effects of opioids given epidurally have also been observed with tramadol. The analgesic period was increased with a combination of caudal tramadol and ropivacaine, but the incidence of nausea and vomiting also increased. On the other hand, the rescue analgesic requirements of the patients decreased with the combination (22).

In an animal study investigating somatosensory evoked potentials (SSEPs), the direct application of tramadol to the sciatic nerve dose-dependently decreased the amplitude and conduction velocity of SSEPs, and it was concluded that tramadol has a local anesthetic effect on peripheral nerves (23). The analgesic effect of tramadol was more potent and of longer duration in a rat plantar injection model. This effect could not be reversed with naloxone and proportionally increased with calcium concentration. These results demonstrated that the local anesthetic effect of tramadol may occur through a different mechanism than lidocaine (7). Tramadol seemed to demonstrate a conduction block similar to lidocaine to a weaker extent (8). Additionally, intrathecal tramadol administration dose-dependently depressed both evoked potentials and motor nerve conduction in rats (24).

The antinociceptive effect of tramadol occurred at spinal and supraspinal levels in a study performed in rats. Some of the activities of tramadol seemed to develop without activating opioid receptors.

Moreover, it has been concluded that tramadol had no local anesthetic activity based on the lack of change in A-β fibers (25). The analgesic effect of tramadol was mediated through μ and α-2 receptors in a study conducted on wild-type and morphine receptor knockout mice (26).

Some limitations of the present study should be mentioned. It was impossible to standardize the perioperative analgesic requirements and consumption, which could have influenced the outcome. In addition, the postoperative analgesic effects were not compared with epidural bupivacaine or different doses, and these topics deserve to be evaluated in further studies. Although no respiratory complications were observed, ventilator parameters were not documented. Furthermore, it was not possible to distinguish the opioid-induced side effects of tramadol from those of fentanyl, the other supplemental analgesic drug. No detailed neurologic evaluation was performed to determine the local anesthetic properties of the study drug due to closure of the surgical site and limited movement in the postoperative period.

Tramadol infiltration before microdiscectomy operations significantly decreased analgesic consumption in the study procedure. Although the depression of hyperpolarization or the local anesthetic and antiinflammatory properties of tramadol might explain its effects, future investigations are required to clarify the issue.

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