Effect of intrathecal tramadol administration on postoperative pain after transurethral resection of prostate

J. A. Alhashemi* and A. M. Kaki

Department of Anesthesia and Critical Care, King Abdulaziz University, King Abdulaziz University Hospital, P.O. Box 31648, Jeddah 21418, Saudi Arabia
*Corresponding author. E-mail: jaalhashemi@hotmail.com

Background. Tramadol administered epidurally has been demonstrated to decrease postoperative analgesic requirements. However, its effect on postoperative analgesia after intrathecal administration has not yet been studied. In this double-blind, placebo-controlled study, the effect of intrathecal tramadol administration on pain control after transurethral resection of the prostate (TURP) was studied.

Methods. Sixty-four patients undergoing TURP were randomized to receive bupivacaine 0.5% 3 ml intrathecally premixed with either tramadol 25 mg or saline 0.5 ml. After operation, morphine 5 mg i.m. every 3 h was administered as needed for analgesia. Postoperative morphine requirements, visual analogue scale for pain at rest (VAS) and sedation scores, times to first analgesic and hospital lengths of stay were recorded by a blinded observer.

Results. There were no differences between the groups with regard to postoperative morphine requirements (mean (SD): 10.6 (7.9) vs 9.1 (5.5) mg, \( P = 0.38 \)), VAS (1.6 (1.2) vs 1.2 (0.8), \( P = 0.18 \)) and sedation scores (1.2 (0.3) vs 1.2 (0.2), \( P = 0.89 \)). Times to first analgesic (6.3 (6.3) vs 7.6 (6.2) h, \( P = 0.42 \)) and length of hospital stay (4.7 (2.8) vs 4.4 (2.2) days, \( P = 0.66 \)) were similar in the two groups.

Conclusion. Intrathecal tramadol was not different from saline in its effect on postoperative morphine requirements after TURP.

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Intrathecal opioid administration has been demonstrated to provide effective postoperative analgesia after a variety of surgical procedures, albeit at the cost of an increased risk for respiratory depression.1 Tramadol, in contrast, is a centrally acting analgesic that has minimal respiratory depressant effects,2,3 by virtue of its 6000-fold decreased affinity for \( \mu \)-receptors compared with morphine.4,5 It also inhibits serotonin and norepinephrine reuptake in the spinal cord and has no reported neural toxicity.6 Accordingly, tramadol has the potential to provide effective postoperative analgesia with no risk of respiratory depression after central neuraxial administration.

Although epidural tramadol has been demonstrated to provide adequate postoperative analgesia in patients undergoing major abdominal surgery and Caesarean section,7,8 its efficacy after intrathecal administration has not yet been studied. Therefore, a randomized, double-blind, placebo-controlled clinical study was undertaken to compare the effect of intrathecal tramadol with that of placebo on postoperative pain after transurethral resection of the prostate (TURP).

Methods

After institutional ethics committee approval (Ethics and Research Committee), 64 ASA class I–III patients gave written informed consent to participation in this randomized, double blind, placebo-controlled clinical trial. Patients were eligible for the study if they were undergoing elective TURP. Exclusion criteria were: transurethral resection of bladder tumour; any contraindication to spinal anaesthesia; and any allergy to the study medication. Using
a computer-generated randomization schedule, patients were randomized to one of two study groups: intrathecal tramadol (group T) or intrathecal normal saline (group S).

In the operating room, all patients were hydrated with normal saline 500 ml and midazolam 20 μg kg⁻¹ i.v. was given after application of standard monitors. Heart rate (HR) and systolic (SBP) and diastolic (DBP) arterial blood pressures were recorded at baseline and every 5 min thereafter until the end of surgery, using the built-in non-invasive blood pressure module of the anaesthesia machine monitor (Cardiocap®; Datex-Ohmeda, Finland). The skin of the back was prepared in the usual fashion, and was anaesthetized locally with lidocaine 2% 3 ml at level L3–4 or L4–5, with the patient in the sitting position. Spinal puncture was performed using a 25-gauge pencil-point spinal needle. All patients received bupivacaine 0.5% 15 mg intrathecally, co-administered in a blinded fashion with either preservative-free tramadol 25 mg 0.5 ml (group T) or preservative-free normal saline 0.5 ml (group S). Fentanyl 25–50 μg i.v. was administered as needed for intraoperative breakthrough pain, and ephedrine 5 mg i.v. was used as needed to treat hypotension (defined as a 20% decrease in systolic blood pressure from baseline value). HR ≤45 beats min⁻¹ was treated with atropine 0.3 mg i.v. as needed.

After operation, pain at rest was assessed using a visual analogue scale (VAS) (0 for no pain, 10 for the worst pain the patient had ever experienced). Level of sedation was determined using the following scale: 1=wide awake; 2=sleepy but easily aroused; 3=sleepy and difficult to arouse. VAS and sedation scores were assessed by a blinded nurse hourly for the first 8 h after operation, and every 4 h thereafter for a total of 24 h. After each pain assessment, patients were asked if they wanted something for pain regardless of their VAS score. In addition, patients were instructed to request pain medication from the nurse if they wanted analgesia and not wait for the next scheduled VAS score assessment. In the postanaesthesia care unit, pain was treated with morphine 2–4 mg i.v. titrated to patient comfort, whereas on the ward it was treated with morphine 5 mg i.m. every 3 h as needed. No other analgesic and/or sedative agents, including non-steroidal anti-inflammatory drugs, were allowed during the first 24 h after surgery. Metoclopramide 10 mg i.m. every 6 h as needed and diphenhydramine 25 mg i.m. every 4 h as needed were prescribed for nausea/vomiting and itching respectively. The amount of morphine administered after operation, time to first analgesic dose, postoperative length of stay and the occurrence of any intraoperative or postoperative adverse events, including (but not limited to) nausea, vomiting, itching, respiratory depression (defined as a respiratory rate <12 bpm) and postdural puncture headache, were documented.

The primary outcome measure (postoperative morphine requirements) and the secondary outcome measures (time to first analgesic, postoperative length of stay, VAS and sedation scores) were analysed using the two-sample t-test.

| Table 1 Patient and surgical characteristics. Data are mean (SD) unless otherwise noted. *P=0.024 compared with group T. S=saline; T=tramadol |
|-----------------------------------------------|-----------------|-----------------|
| Age (range) (yr) | 66.4 (42–96) | 65.8 (40–87) |
| Weight (kg) | 74.9 (16.3)* | 67.0 (9.4) |
| Height (cm) | 167.3 (9.5) | 163.6 (10.6) |
| ASA class I/II/III (n) | 11/18/3 | 5/23/4 |
| Median (range) anaesthesia time (min) | 62.5 (20–160) | 60.0 (30–120) |
| Patients requiring ephedrine | 5 | 3 |
| Dose of ephedrine required (mg) | 6.6 (2.9) | 6.7 (2.1) |

VAS and sedation scores and intraoperative SBP, DBP and HR were analysed using repeated measures analysis of variance (RM-ANOVA) to detect differences over time. Any imbalance in the patients’ characteristics was adjusted for by performing multivariate regression analysis that included the variable in question as an independent variable. All statistical procedures, except RM-ANOVA, were performed using the Minitab® software package, release 12.23 for Windows® (Minitab, State College, PA, USA). SPSS® statistical software (SPSS, Chicago, IL, USA), version 9.0 for Windows, was used for RM-ANOVA. Results are presented as mean (SD) unless otherwise indicated, and statistical significance was defined as P<0.05. Post hoc power analysis was performed using the pooled variance that was estimated from the study, an α value of 0.05, and a difference of 5 mg in postoperative morphine requirements. The study had an 82% power to detect a difference of 5 mg in postoperative morphine requirements between the study groups.

**Results**

Patient characteristics were similar in the two study groups, except for body weight (P=0.024) (Table 1). None of the patients in either group required any intraoperative fentanyl, atropine or supplementary anaesthesia. There was no difference in postoperative morphine requirements between the groups (P=0.38) (Table 2). After adjusting for the potential confounding effect of weight, there was still no difference between the two groups in the amount of morphine received after operation (P=0.79). When the cumulative doses of morphine administered over the first 4 and 8 h after operation were compared between the study groups, there were no differences in the amounts of morphine administered (P=0.21 and 0.64 respectively) (Table 2). Sedation scores were comparable between the study groups (P=0.89). In contrast, a trend towards increased VAS score in group S was observed (P=0.18). However, there were no differences in VAS or sedation scores over time between the two study groups (P=0.6 and 0.37 respectively) (Figs 1 and 2). In addition, there were no differences over time between the groups with regard to SBP and DBP (P=0.46 and 0.72 respectively) (Figs 3 and 4).
On the other hand, there was a trend towards increased HR in group T compared with group S \( (P=0.15) \) (Fig. 5). Haemodynamic data could be analysed only up to 75 min intraoperatively as the number of patients fell dramatically beyond this time. Times to first analgesic dose and postoperative lengths of stay were similar in the two groups \( (P=0.42 \text{ and } 0.66 \text{ respectively}) \) (Table 2). Postoperative adverse events were rare and their frequency was comparable in the two study groups (Table 3).

**Discussion**

Tramadol is a centrally acting analgesic agent with two distinct mechanisms of action. It binds opioid receptors weakly and inhibits the reuptake of norepinephrine and serotonin in the spinal cord.\(^4\)\(^9\) The drug has a terminal elimination half-life of 5.5 h and provides clinical analgesia for 4–6 h after parenteral administration and for 10 h after epidural administration.\(^10\) When administered epidurally, tramadol has been demonstrated to provide adequate postoperative analgesia after major abdominal surgery and Caesarean section.\(^5\)\(^8\) However, its effect on postoperative pain after subarachnoid administration is still unknown. This randomized, double-blind, placebo-controlled study demonstrated that intrathecal tramadol in a dose of 25 mg was ineffective in decreasing analgesic requirements after TURP surgery. Although body weight was not balanced between the two study groups, it had no effect on the results of the study, as evidenced by the adjusted analysis. Post hoc power analysis indicated that the study had an 82% power to detect a difference of 5 mg in mean postoperative morphine requirements between the study groups.

The failure of intrathecal tramadol in providing effective postoperative analgesia could be attributed to a number of factors. First, the tramadol dose used in this study could have been too small for a clinically relevant analgesic effect to be detected. The rationale for using this dose, though, was the fact that tramadol has analgesic potency similar to that of meperidine,\(^2\) and a similar dose of intrathecal meperidine has been demonstrated to decrease the analgesic requirement after TURP.\(^11\) Furthermore, a larger dose of tramadol may have increased the incidence of postoperative nausea and/or vomiting, as has been reported previously.\(^12\) Whether a larger dose of intrathecal tramadol would have reduced the postoperative analgesic requirement remains to be determined. Secondly, tramadol has decreased affinity for \( \mu \)-receptors,\(^4\)\(^5\) which are the site of action for spinally administered opioids. Thus, it is conceivable that the
analgesic efficacy of tramadol could decrease after intrathecal administration. In support of this are the findings of Grace and Fee, who failed to demonstrate analgesic efficacy of epidurally administered tramadol in patients undergoing total knee replacement. In contrast, other investigators have reported adequate postoperative analgesia after epidural tramadol administration. However, in all these studies epidural tramadol was administered in the dose recommended for the i.v. route. As epidurally administered opioids exert their analgesic effects via systemic absorption and diffusion into the spinal cord, it is likely that the observed analgesic effect of epidural tramadol in these positive studies is secondary to systemic uptake of tramadol from the epidural space and consequent achievement of therapeutic plasma concentrations of the drug. Furthermore, a single i.v. dose of tramadol 150 mg has produced an analgesic effect comparable to that of epidural morphine in patients undergoing thoracotomy. Thirdly, it is possible that the lipophilic properties of tramadol resulted in rapid diffusion of the drug out of the subarachnoid space. This rapid drug clearance from the subarachnoid space has been reported for fentanyl and sufentanil and has been attributed to their lipophilicity. Finally, on the basis of the duration of tramadol-induced analgesia, it is possible that the analgesic effects of tramadol had disappeared before the spinal anaesthetic had regressed. The absence of a reference group in which intrathecal tramadol was administered as the sole agent precludes proof or refutation of this hypothesis.

Another possible explanation for the negative results of this study is the suggestion of Wilder-Smith and colleagues that epidural tramadol in a dose of 20 mg may have anti-analgesic effects. As epidurally administered opioids do not exert their pharmacological effects in the epidural space, any anti-analgesic effect of tramadol would probably be mediated via its systemic action or its effect on the spinal cord. In the present study, tramadol was administered intrathecally in a dose similar to that used in the study of Wilder-Smith and colleagues. If the specific monoaminergic effects of this small dose of intrathecal tramadol had counteracted its direct weak opioid effect on the spinal cord with consequent anti-analgesia, this could explain the observed failure of the drug in decreasing postoperative morphine requirements. Further studies are needed to confirm this hypothesis and to determine the exact underlying mechanism, if any.

Times to first analgesic request and the amounts of morphine administered over the first 4 and 8 h after operation were all comparable between the two study groups, which suggests that tramadol did not potentiate the

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**Fig 3** Changes in intraoperative systolic blood pressure over time. S=saline; T=tramadol. Mean and SD.

**Fig 4** Changes in intraoperative diastolic blood pressure over time. S=saline; T=tramadol. Mean and SD.

**Fig 5** Changes in intraoperative heart rate over time. S=saline; T=tramadol. Mean and SD.

**Table 3** Postoperative adverse events. There were no significant differences in complications. S=saline; T=tramadol

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<thead>
<tr>
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<th>Group S (n=32)</th>
<th>Group T (n=32)</th>
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</thead>
<tbody>
<tr>
<td>Intraoperative nausea/vomiting (n)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative nausea/vomiting (n)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Pruritus (n)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Postdural puncture headache (n)</td>
<td>0</td>
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<td>Respiratory depression (n)</td>
<td>0</td>
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<tr>
<td>Neurological complications (n)</td>
<td>0</td>
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local anaesthetic effects of bupivacaine. This is in keeping with the results of Gunduz and colleagues, who found that tramadol does not prolong the duration of action of bupivacaine when the drugs are co-administered caudally. However, our study was not powered adequately to detect such a difference, as this was a secondary outcome measure. In contrast to these results, Kapral and colleagues have reported that the addition of tramadol 100 mg to mepivacaine 1% for brachial plexus anaesthesia prolongs the duration of the block when compared with placebo. This, nonetheless, could be attributed to the local anaesthetic-like effects of tramadol on peripheral nerves.

Intraoperative SBP and DBP were comparable in the study groups. However, there was a trend towards increased HR in patients who received tramadol. The study was not powered to detect differences in haemodynamic profiles as these were secondary outcome measures. Furthermore, the magnitude of increase in HR in group T was not clinically relevant (Fig. 5). Accordingly, intrathecal tramadol did not seem to influence the intraoperative haemodynamic profile of patients undergoing this type of anaesthetic. These results are in keeping with those reported previously by other investigators who have demonstrated that parenteral tramadol does not have clinically relevant effects on HR and blood pressure.

A limitation of the present study is the fact that postoperative analgesia was administered, on demand, by the nurse by i.m. injection. This was in accordance with our institutional policy, whereby nurses on the ward are not allowed to administer analgesics i.v. The observed trend towards higher VAS scores in patients who received saline (P=0.18) suggests that this limitation of nurse-administered analgesia might have masked small differences in postoperative morphine requirement between the study groups. However, the generally low mean VAS scores observed in both groups (1.6 and 1.2) would make such a difference clinically irrelevant, even if it had achieved statistical significance.

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