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Increased nausea and dizziness when using tramadol for post-operative patient-controlled analgesia (PCA) compared with morphine after intraoperative loading with morphine

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Summary

Thirty-eight ASA I–III patients undergoing lower abdominal operations were randomly allocated to receive either morphine (group M, patient-controlled analgesia bolus = 1 mg of morphine) or tramadol (group T, patient-controlled analgesia bolus = 10 mg of tramadol) for post-operative patient-controlled analgesia (PCA) after receiving morphine intraoperatively. There were no between-group differences in the pain, sedation or vomit scores. The nausea scores were significantly higher in group T in the initial 20 h and between 32 and 36 h ($P < 0.01$, 0–4 and 8–12 h; $P < 0.05$,

4–8, 12–16, 16–20 and 32–36 h). The incidence of dizziness was also significantly higher in group T (68.4% vs. 31.6%, group T vs. group M, $P < 0.05$). There was no difference in the overall satisfaction. We conclude that the use of tramadol, compared with morphine, for post-operative PCA after intraoperative loading with morphine is associated with more nausea and dizziness, but with similar sedation, quality of analgesia and patient satisfaction.

Keywords: ANALGESIA, patient-controlled, tramadol, morphine; SURGERY, lower abdominal.

Introduction

Tramadol is an effective opioid analgesic. It may be superior to other 'conventional' opioids such as morphine and pethidine when used as a post-operative analgesic because of its relative lack of sedative and respiratory depressive effects at clinically effective doses [1,2]. Intraoperative loading with tramadol, however, may be undesirable because of the possibility of awareness associated with its use [3]. We designed this study to evaluate in a randomized, double-blind manner the efficacy and side-effect profile of tramadol used as an alternative to morphine for post-operative, patient-controlled analgesia (PCA) after intraoperative loading with intravenous morphine.

Materials and methods

The study was approved by the institutional ethics

committee. All patients gave informed written consent to participate in the study. Patients <18 years old, of ASA class IV or above, not mentally fit for the operation of PCA, who requested other post-operative analgesic techniques, with known allergy to morphine or tramadol, with known history of substance or alcohol abuse, and pregnant or lactating women were excluded.

There were two treatment groups. All patients received patient-controlled intravenous injection of analgesics via a Graseby 3300 PCA pump (Graseby Medical Ltd, Watford, UK) for post-operative analgesia. In the morphine group (group M), patients had morphine 1 mg mL⁻¹ in 0.9% sodium chloride solution in their pump. In the tramadol group (group T), patients had tramadol 10 mg mL⁻¹ in 0.9% sodium chloride solution. The dose ratio of tramadol to morphine of 10:1 was based on previous reports [1,2]. All pumps were set to an identical setting with a PCA bolus of 1 mL (corresponding with morphine 1 mg in group M and tramadol 10 mg in group T). No basal infusion

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was prescribed. The lockout intervals were all set at 5 min. In both groups, patients were prescribed on an 'as required' basis, metoclopramide 10 mg intravenously and pethidine 0.4 mg kg⁻¹ intramuscularly every 4 h as the rescue antiemetic and analgesic respectively.

Eligible patients were allocated randomly to one of the two treatment groups according to random pick of sealed envelopes at the end of the operation. Both the patients and the nurses responsible for post-operative care and observation of the patients were blinded to the grouping of the patients.

All patients were given instructions on the use of PCA during the preoperative assessment and brought to theatre with no premedication. General anaesthesia was induced with thiopentone 4–5 mg kg⁻¹, a single bolus dose of 50–100 µg of fentanyl and a loading dose of atracurium 0.5–0.6 mg kg⁻¹ or vecuronium 0.1 mg kg⁻¹. The patients' tracheas were then intubated and intermittent positive pressure ventilation started. Anaesthesia was maintained with a mixture of O₂, N₂O plus enflurane or isoflurane. Atracurium or vecuronium were used for muscle paralysis by continuous infusion. All patients received incremental intravenous doses of morphine for intraoperative analgesia. The dose was decided by the attending anaesthetist. Intraoperative use of tramadol was avoided because of concern over the possibility of an increased risk of awareness [3]. At the end of the procedure, the study drug was prepared by the attending anaesthetist according to the instruction in the envelope. The syringes were labelled as 'study opioid' and put into patients' PCA pumps. All nurses in the recovery room and in the wards were blinded to the type of opioid used. The patients were then extubated and sent to the recovery room where PCA was started.

When analgesia was required in the recovery room, patients would either activate the PCA pumps themselves or, if they were still drowsy, the recovery room nurses would activate the pump for them. Patient observation, which was carried out by nurses, was also started in the recovery room and continued in the wards. Vital signs including blood pressure (BP), pulse (P), oxygen saturation (SpO₂) and respiratory rate (RR) were recorded. Arterial blood gas was checked if RR < 10 or clinically indicated. Analgesia was assessed by a verbal rating scale (VRS) from 0 to 10, hourly in the first 24 h after operation, and 4-hourly

Table 1. Scoring for nausea, vomit and sedation

Condition	Scoring criteria
Nausea	0 = no nausea 1 = mild nausea, patient not requesting metoclopramide 2 = nausea, patient requesting metoclopramide 3 = nausea resistant to metoclopramide
Vomit	0 = no vomit 1 = mild vomit, patient not requesting metoclopramide 2 = vomit, patient requesting metoclopramide 3 = vomit resistant to metoclopramide
Sedation	0 = fully awake 1 = slightly drowsy 2 = sleeping but easily arousable 3 = unconscious, not arousable

thereafter. Nausea and vomiting were assessed on two separate four-point scoring scales and degree of sedation on another four-point scale (Table 1). All these observations were made every 4 h. In addition, the total number of times the patients activated the pump ('tries'), the number of pump activations that actually resulted in drug delivery ('goods'), the ratio of these two numbers ('tries/goods' ratio) and the total dose of drug consumed were recorded daily. Use of rescue analgesic or antiemetic and other symptoms such as dizziness, headache, dry mouth and other discomfort were also recorded daily. An overall assessment of the analgesic technique as good, fair or unsatisfactory was given by the patients on discontinuation of the PCA pump. Any major complications, defined as a sedation score of 3, RR < 8 and P_aCO₂ > 6.7 kPa, or patients requiring re-intubation and ventilatory support or SpO₂ < 90% for > 5 min with optimal O₂ therapy by mask were recorded. The patients were also followed up daily by an anaesthetist from the pain management team. However, the pain management team physician was only responsible for the clinical well-being of the patients. They did not contribute to the entry of any data that would subsequently be analysed in this study. Whenever the analgesic or the setting on the PCA pump was changed, the patient was excluded from the study.

The PCA pumps were used by the patients for at least 48 h unless they requested discontinuation before this. The reason for discontinuation was recorded under such circumstances. Refilling of the syringes was done by one of the investigators to keep the nurses on the wards blinded. If patients still wanted the PCA pump after 48 h, they were allowed to continue with PCA.

The sample size of 19 in each group was able to detect with 80% power an intergroup difference in nausea, vomit or sedation score of 1, assuming a standard deviation of 1 at an α -error level of 0.05.

Statistical analysis was performed using the software programme Statistica release 4.5 (StatSoft, Tulsa, OK, USA). Non-parametric data such as nausea and vomit scores, pain score, number of demands on PCA pump and patient demographic variables were analysed by Mann-Whitney *U*-test and chi-squared test as appropriate. Parametric data were compared by two-tailed independent *t*-tests. Significance level was set at $P < 0.05$.

Results

A total of 39 patients were studied, 19 in group T and 20 in group M. One patient in group M was excluded from the study in the early post-operative period because of complications (detailed below). Limited data were available from this patient, and he was excluded from the analysis. Patient demographics, operation duration, amount of blood loss and the dose of intraoperative morphine administered are summarized in Table 2.

No differences were observed in the 4-hourly pain scores in the two treatment groups throughout the study period (Fig. 1). The average hourly demands made on the PCA pump, the ratio of total demands to 'good' demands (tries/goods ratio) and the number of requests for rescue analgesic during the study period were also not different. These are summarized in Table 3. No patient was excluded from the study because of inadequate analgesia necessitating changes in the PCA regime. The hourly consumption of morphine was 1.05 mg (0.68–1.41 mg, 95% CI), and that of tramadol was 9.79 mg (6.71–12.86 mg, 95% CI) during the study period. This gives a dose ratio of about 1:9.3 for intravenous morphine to tramadol.

Patients in group T had significantly higher nausea scores in the initial 20 h, as well as between 32 and

Table 2. Demographic data and operative details

Group	M (n=19)	T (n=19)
Age (years)	59.26 (18.02)	57.68 (13.90)
Sex (M/F)	10/9	7/12
Body weight (kg)	52.57 (9.51)	56.58(10.27)
ASA I*	7 (37%)	5 (26%)
ASA II	9 (47%)	12 (63%)
ASA III	3 (16%)	2 (11%)
Operation duration (min)	153.68 (51.45)	142.11 (60.99)
Blood loss (mL)	418.82 (457.60)	478.75 (379.95)
Intraoperative morphine (mg)	7.00 (3.09)	7.73 (2.95)

Values are means (SD).

*Number (percentage).

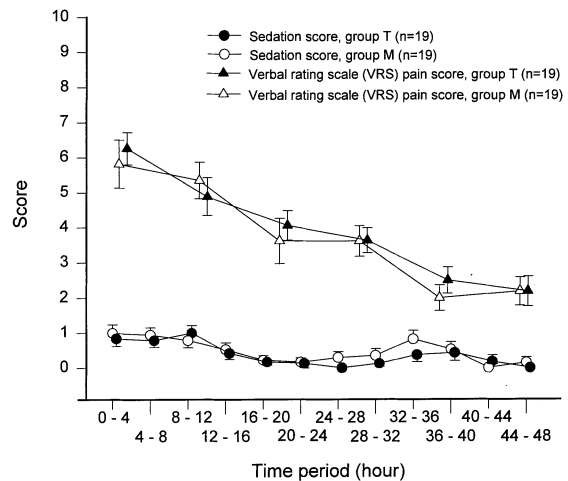


Fig. 1. Verbal rating scale (VRS) pain scores and sedation scores. Values are means \pm SEM. There were no between-group differences throughout the study (Mann-Whitney *U*-test for between-group comparison).

36 h after operation (Fig. 2). However, there were no differences in the vomit scores (Fig. 3). Two patients required metoclopramide in group M (10.5%) and seven patients in group T (36.8%). The difference was not significant ($P=0.13$, chi-squared test with Yates' correction). Significantly more patients in group T (68.4%) experienced some dizziness during the study period than those in group M (31.6%) ($P < 0.05$, chi-squared test).

There were no differences in the sedation scores throughout the study period. The mean sedation scores are summarized in Fig. 1. Whereas no major

Table 3. Analgesic requirement during the study period

Group		M (n=19)	T (n=19)	P-value
Hourly demands made		1.89 (1.89)	2.80 (4.55)	NS
Tries/goods ratio	0-24 h	2.55 (2.56)	2.85 (2.02)	NS
	24-48 h	1.61 (0.71)	1.84 (1.30)	NS
Request for rescue analgesic*	None	17 (89%)	17 (89%)	NS
	Once	1 (5%)	1 (5%)	
	Twice	0	0	
	> Twice	1 (5%)	1 (5%)	

Values are means (SD).

*Number (percentage).

Request for rescue analgesic analysed by Mann-Whitney U-test.

Tries/goods ratio and hourly demands analysed by Student's t-test.

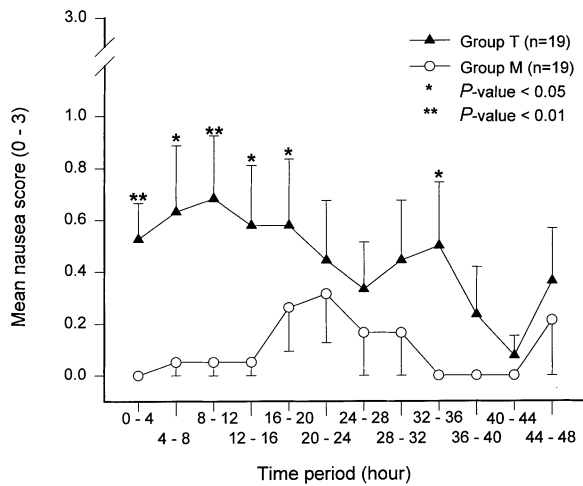


Fig. 2. Four-hourly nausea scores. Values are means ± SEM. Nausea scores were significantly higher in group T in the initial 20 h and between 32 and 36 h (Mann-Whitney U-test for between-group comparison).

complication occurred in the group T patients, two patients in group M became deeply sedated (sedation score of 3). Both episodes occurred in the initial 4 h after operation. One of these patients also developed CO₂ retention. Intravenous naloxone was administered to this patient, the setting on the PCA pump was reduced, and the patient was excluded from the study. There were no differences in the BP, P, RR and SpO₂ between the two groups throughout the study.

Eleven patients (57.9%) rated their PCA experience as good overall, seven (36.8%) as fair and one (5.3%) as bad in group M. Fifteen (78.9%) patients rated good, three (15.8%) rated fair and one (5.3%) rated bad in

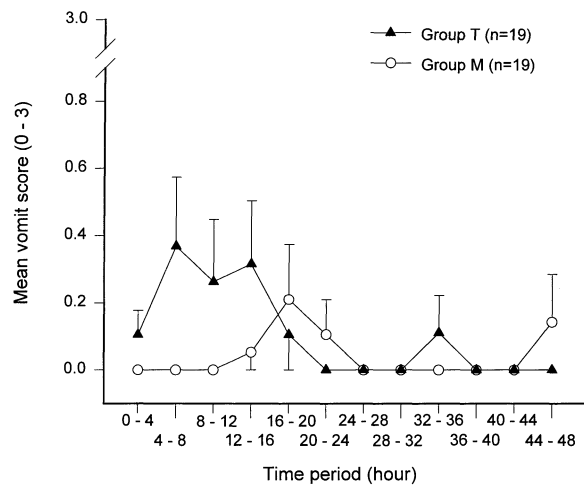


Fig. 3. Four-hourly vomit scores. Values are means ± SEM. There were no between-group differences throughout the study (Mann-Whitney U-test for between-group comparison).

group T. The differences were not significant ($P=0.26$, Mann-Whitney U-test).

Discussion

The results of our study demonstrated a similar quality of analgesia and degree of patient satisfaction using tramadol for post-operative PCA when compared with morphine in a group of patients after lower abdominal surgery. In the largest study to date comparing intravenous tramadol and morphine for post-operative analgesia in a non-PCA setting, Vickers *et al.* [1]. have also found similar efficacy of the two drugs. A single

intravenous bolus dose of tramadol has also been demonstrated to offer comparable analgesia to epidural morphine after thoracotomy with combined general and epidural anaesthesia [4]. The use of tramadol in PCA has also been compared with PCA pethidine [5] with satisfactory results. There is little doubt that tramadol is an effective intravenous analgesic for use in the post-operative period administered either as a bolus or via a PCA pump.

Unlike other 'conventional' opioids, the mechanism of action of tramadol involves not only the μ -receptor, but also inhibition of 5-HT and noradrenaline reuptake in the central nervous system [6]. In fact, the analgesic effect of tramadol can only be partially reversed by naloxone [6]. These multiple sites of action may account for the potential benefit of tramadol when used as a post-operative analgesic, namely the lower risk of respiratory depression [2]. In the present study, one patient receiving morphine developed respiratory depression requiring naloxone. Although no statistically significant difference can be demonstrated regarding the incidence of respiratory depression between the two groups, this is most probably because of the low power of our sample when looking at rare events such as respiratory depression. Bakhshi *et al.* [7] have demonstrated a lower incidence of desaturation when tramadol is used post-operatively when compared with morphine.

Our present study demonstrated an increased incidence of dizziness and increased incidence and severity of nausea in patients receiving PCA tramadol compared with PCA morphine. The difference in nausea was most marked in the initial 12 h after the operation. This was not observed in previous studies in which intraoperative morphine had not been used [1,5]. One possible explanation for our observation is that there may be 'synergism' between the residual effect of intraoperative morphine and that of subsequently administered tramadol in terms of causing nausea and dizziness in the initial post-operative period. Given the multiple sites of action of tramadol, it is quite likely that its effect on nausea and vomiting is also mediated via receptors other than the opioid receptor and, therefore, compounded by the concomitant use of other opioids. 5-HT reuptake inhibition, for instance, could be responsible for this complication.

We considered adequate opioid loading intraoperatively an essential part of perioperative pain management. Patients should have adequate analgesia emerging from anaesthesia. This increased patient comfort in the recovery room and smoothed out the transition to using PCA post-operatively. In our institution, intravenous morphine is the conventional technique for intraoperative analgesia under general anaesthesia. We have chosen not to use short-acting opioids such as alfentanil intraoperatively in our study. Unless we allowed our patients to emerge from anaesthesia in pain, irrespective of whether we used a short- or long-acting opioid intraoperatively, patients needed to have residual opioid activity in the initial post-operative period. We decided to use morphine intraoperatively even for the tramadol group because of the possible association between the intraoperative use of tramadol and awareness under general anaesthesia, although the evidence in the literature is not conclusive [3,8].

In contrast to previous studies, we were unable to demonstrate less patient sedation in the tramadol group. This might be related to the difference in the route of administration, namely by PCA in the present study. The small sample size may also contribute to this. Another possibility is the residual sedating effect of intraoperative morphine, which would mask any difference in sedation, at least in the early post-operative period. Any difference in sedation, if present, should be most obvious in this period.

We conclude from our study that tramadol is comparable with morphine when used in post-operative PCA in terms of safety and efficacy following lower abdominal operations. However, the concomitant use of intravenous morphine intraoperatively is associated with a more frequent incidence of nausea and dizziness. Further investigations are required to overcome this problem. For example, the use of prophylactic antiemetics acting via 5-HT₃ antagonism may be useful, given the inhibitory effect of tramadol on 5-HT reuptake. At present, it seems prudent to avoid loading with morphine if tramadol is to be used for post-operative analgesia.

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