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Pre-emptive analgesic efficacy of tramadol compared with morphine after major abdominal surgery

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Background. Studies of pre-emptive analgesia in humans have shown conflicting results. This prospective, randomized, double-blind, controlled study was designed to test the hypothesis that a reduction in postoperative morphine consumption can be achieved by tramadol administered after induction of anaesthesia.

Methods. Ninety patients were allocated randomly to receive i.v. tramadol (1 mg kg^{-1}) (Group T), morphine (0.1 mg kg^{-1}) (Group M) or saline 2 ml (Group S) after induction of anaesthesia. At peritoneal closure, a standardized (0.1 mg kg^{-1}) morphine loading dose was given to all patients for postoperative pain management. Patients were allowed to use a patient-controlled analgesia (PCA) device giving bolus doses of morphine 0.025 mg kg^{-1}. Discomfort, sedation, pain scores, cumulative morphine consumption, and side-effects were recorded at 1, 2, 6, 12 and 24 h after the start of PCA.

Results. There were no significant differences between groups in mean pain, discomfort, and sedation scores at any study period. Cumulative morphine consumption was significantly lower in Group M at 12 and 24 h after starting the PCA than in Group S. In Group T, it was lower only after 24 h (28% less in Group M and 17% less in Group T; $P<0.017$). There were no significant differences in morphine consumption between Groups T and M.

Conclusions. Tramadol (1 mg kg^{-1}), administered after induction of anaesthesia, offered equivalent postoperative pain relief, and similar recovery times and postoperative PCA morphine consumption compared with giving morphine 0.1 mg kg^{-1}. These results also suggest that presurgical exposure to systemic opioid analgesia may not result in clinically significant benefits

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Tramadol hydrochloride is a synthetic μ-opioid agonist which also has monoaminergic activity, exerted via inhibition of neuronal uptake of serotonin and norepinephrine.[1] Administered i.v., its analgesic potency is the same as meperidine and one-tenth that of morphine.[2] However, its affinity for μ-opioid receptors (6000 times less than that of morphine) cannot account for its antinociceptive potency.[3 4]

Although several studies have addressed the antinociceptive effect of tramadol for treatment of postoperative pain, its pre-emptive analgesic effect in the treatment of postsurgical pain is not clear.[5 6] Pre-emptive analgesia is defined as 'analgesic intervention provided before surgery to prevent or reduce subsequent pain'.[7] This effect has been demonstrated in animal experiments but, while some clinical results have supported the concept, others have failed to show any effect.[7] Two reports suggest that postoperative morphine consumption is reduced when morphine is given at the start of surgery rather than at the end.[8 9]

This prospective, randomized, double-blind, controlled study was designed to test whether a similar reduction in postoperative morphine consumption can be achieved by giving tramadol. The hypothesis was that, in patients who underwent major abdominal surgery, tramadol, administered after induction of anaesthesia, would allow earlier recovery after anaesthesia, equivalent postoperative pain relief and similar postoperative PCA morphine consumption compared with morphine.

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Table 1 Patient characteristics, type of surgery, duration of anaesthesia, requirement for supplemental meperidine, time to extubation, and time to recovery. Data are presented as mean (95% CI) or number (%). *$P<0.017$ between Group S and Group M by Mann–Whitney *U*-test

	Group S (*n*=30)	**Group T (*n*=30)**	**Group M (*n*=30)**
Age (yr)	47.2 (38.1–56.2)	46.1 (38.8–53.3)	49.8 (43.4–56.1)
Sex M/F (*n*)	13/17	14/16	14/16
Weight (kg)	68.6 (59.0–78.1)	66.2 (55.9–76.4)	65.6 (55.5–75.6)
Duration of anaesthesia (min)	131.2 (123.4–138.5)	126.2 (118.7–133.6)	130.8 (123.8–137.7)
Number of patients requiring supplemental meperidine (*n*)	4 (13.3)	3 (10)	3 (10)
Time to extubation (min)	4.9 (4.2–5.6)	5.6 (4.8–6.4)	6.8 (6.3–7.3)*
Time to recovery (min)	7.9 (7.0–8.7)	8.4 (7.8–9.0)	9.2 (8.4–10.0)*
Type of surgery (*n*)			
Upper gastrointestinal	12 (40)	11 (36)	10 (33)
Lower gastrointestinal	10 (33)	14 (46)	12 (40)
Hepato-pancreatico-biliary	8 (27)	5 (18)	8 (26)

Patients and methods

Following ethics committee approval and informed patient consent, 90 ASA I or II patients, between the ages of 21 and 58 yr, undergoing elective major abdominal surgery with general anaesthesia, were recruited. Before surgery, patients were instructed on the use of the PCA device and the verbal rating scale (VRS) for pain assessment. Exclusion criteria included inability to use the PCA device, long-term use of opioid medications, and a history of chronic pain. All patients were premedicated with i.v. midazolam 0.1 mg kg^{-1} 30 min before surgery. Intraoperative monitoring included pulse oximetry, automated blood pressure cuff, and lead II ECG.

Anaesthesia was induced with thiopental sodium 5 mg kg^{-1} and maintained with sevoflurane 1.5–2% in a mixture of nitrous oxide 66% and oxygen 34%. Neuromuscular block was induced by i.v. boluses of vecuronium bromide (0.1–0.2 mg kg^{-1}) and maintained (0.03 mg kg^{-1}) by bolus administration at 30 min intervals. After induction of anaesthesia, patients were allocated randomly to receive one of three study drugs, to be used after induction of anaesthesia but before surgical intervention. The drugs were prepared by an anaesthetist, who was not one of the observers, in three 2-ml syringes, which contained either 1 mg kg^{-1} tramadol HCl (Grünenthal GmbH, Germany), 0.1 mg kg^{-1} morphine HCl (Galen Corporation, Istanbul, Turkey) or saline 0.9%. They were marked only with a coded label to maintain the double-blind nature of the study. Thus, after induction of anaesthesia, patients in Group T (n=30) received i.v. 1 mg kg^{-1} tramadol, Group M (n=30) received 0.1 mg kg^{-1} morphine, and Group S (n=30) received saline 0.9% before surgical intervention.

A standardized (0.1 mg kg^{-1}) loading dose of morphine was given to all patients at the beginning of closure of the peritoneum. At the end of surgery, patients were extubated after antagonism of residual neuromuscular block with neostigmine (0.05 mg kg^{-1}) and atropine (0.015 mg kg^{-1}). No opioids were administered intraoperatively except for the tramadol or morphine according to the study procedure.

After total recovery from anaesthesia (as judged by the ability to open the eyes, grip a finger, and breathe deeply on request), whenever patients complained of pain, they were allowed to use a morphine PCA (Abbott Pain Management Provider, Class II, Type CF, North Chicago, IL, USA). The settings were i.v. morphine, bolus dose 0.025 mg kg^{-1}, with a lock-out time of 20 min and no background infusion or maximal dose. The PCA settings were determined by the anaesthetist.

Ondansetron 4 mg and meperidine 0.4 mg kg^{-1} were prescribed i.v. every 4 h on request as the rescue antiemetic and analgesic respectively for all patients. The PCA pump was removed 24 h after surgery, at which time i.v. dipyrone (methamizole), 3 g per day, was prescribed for pain management. The cumulative dose of morphine was recorded at 1, 2, 6, 12 and 24 h after administration. It was also planned that if the patients' clinical condition necessitated any change in the analgesic technique or resetting of the PCA pump, the patient would be excluded from the study.

Scores for discomfort, pain, sedation and haemodynamic variables [systolic blood pressures (SBP), diastolic blood pressures (DBP), heart rate (HR) and peripheral oxygen saturation (Sp_{O_2})] were recorded at rest by an anaesthetist in the Pain Management Team, who was blinded to the patient group, at 1, 2, 6, 12 and 24 h after administration.

Discomfort was assessed using an 11-point numerical scale (0=none, 10=extreme discomfort), pain was assessed by a verbal rating scale (VRS) from 0 to 10 (0=no pain, 10=the worst pain imagined) and sedation was assessed using a 5-point scale with 1=alert and 5=deep sleep.[10] Type of surgery, duration of anaesthesia, number of patients requiring supplementary meperidine, time to extubation, time to recovery, and any side-effects (such as nausea and vomiting, pruritis, or urinary incontinence) associated with the procedure were also recorded.

Sample size calculation was based on a power analysis. In the literature,[11] a 30% reduction in morphine consumption is regarded as a clinically significant result. At a power of 0.8 using a significance level of $P<0.05$, the sample size

Table 2 Pain scores (VRS), sedation scores, discomfort scores and mean cumulative morphine consumption in groups at 1, 2, 6, 12 and 24 h after PCA administration. Data are presented as mean (SD) (median (min–max)). *P<0.017 between Group S and Group T by Mann–Whitney U-test; †P<0.017 between Group S and Group M by Mann–Whitney U-test; [a]P<0.05 within groups by Friedman test; [b]Kruskal–Wallis test between three groups

	1st hour	2nd hour	6th hour	12th hour	24th hour
VRS					
Group S	4.7 (1.1) [2 (3–8)]	3.1 (1.1) [2 (2–6)][a]	1.9 (0.9) [1 (1–4)][a]	1.3 (0.6) [1 (1–3)][a]	1.2 (0.4) [1 (1–2)][a]
Group T	4.5 (0.8) [4 (3–6)]	2.9 (1.2) [2 (1–5)][a]	1.6 (0.7) [1 (1–4)][a]	1.2 (0.4) [1 (1–2)][a]	1.0 (0.2) [1 (1–2)][a]
Group M	4.1 (1.1) [5 (2–6)]	2.0 (0.5) [2 (1–3)][a]	1.5 (0.5) [1.5 (1–2)][a]	1.0 (0.2) [1 (1–2)][a]	1.0 (0.1) [1 (1–2)][a]
P-value[b]	0.1	0.09	0.08	0.04	0.03
Sedation					
Group S	1.7 (0.6) [2 (1–3)]	1.3 (0.4) [1 (1–2)][a]	1.0 (0.1) [1 (1–2)][a]	1.0 (0) [1 (1–1)][a]	1.0 (0) [1 (1–1)][a]
Group T	1.8 (0.6) [2 (1–3)]	1.4 (0.5) [1 (1–3)][a]	1.2 (0.4) [1 (1–3)][a]	1.0 (0) [1 (1–2)][a]	1.0 (0) [1 (1–1)][a]
Group M	2.0 (0.6) [2 (1–3)]	1.5 (0.5) [1.5 (1–2)][a]	1.0 (0.1) [1 (1–2)][a]	1.0 (0.1) [1 (1–2)][a]	1.0 (0) [1(1–1)][a]
P-value[b]	0.1	0.3	0.06	0.6	0.9
Discomfort					
Group S	4.7 (1.0) [4(2–6)]	3.1 (0.8) [3 (2–4)][a]	1.9 (0.5) [2 (1–3)][a]	1.1 (0.3) [1 (1–2)][a]	1.0 (0.2) [1(1–2)][a]
Group T	4.0 (1.4) [4 (2–6)]	3.1 (1.1) [3 (1–6)][a]	2.1 (0.8) [2 (1–4)][a]	1.3 (0.4) [1 (1–2)][a]	1.2 (0.5) [1 (1–3)][a]
Group M	4.7 (1.1) [5 (2–6)]	3.5 (0.9) [4 (2–5)][a]	2.3 (0.8) [2 (1–5)][a]	1.5 (0.6) [1 (1–3)][a]	1.2 (0.4) [1 (1–2)][a]
P-value[b]	0.05	0.17	0.14	0.03	0.2
Morphine cumulative (mg)					
Group S	9.0 (1.0) [9.1 (6–11)]	12.5 (0.6) [12.9(9–20)][a]	18.3 (5.5) [17.2(6–30)][a]	28.1 (5.3) [26(23–40)][a]	46.5 (1.7) [47(43–51)][a]
Group T	9.1 (1.0) [5 (7–12)]	12.5 (1.9) [12.8(8–15)][a]	17.6 (4.6) [16(11–31)][a]	25.1 (5.3) [24(15–36)][a]	38 (6.5) [39.5(26–49)]*[a]
Group M	8.9 (1.3) [8.8(7–12)]	12.5 (0.6) [12(11–14)][a]	15.4 (1.9) [15(12–20)][a]	24.5 (0.9) [24(23–27)]†[a]	33.3 (7.5) [34(19–47)]†[a]
P-value[b]	0.8	0.03	0.03	0.004	0.000

required was 30 subjects per study group. The primary endpoint was defined as 24-h morphine consumption via PCA.

Statistical analyses were performed using the statistical package SPSS v9.0. Continuous variables were analysed using one-way ANOVA. As the data were not distributed normally (tested by the Shapiro–Wilk test and evaluated histograms of variables), a non-parametric test was chosen. Ordinal data (VRS, sedation, and discomfort values) were analysed using the Kruskal–Wallis test. As analysis of variance was significant, comparisons were applied using the Mann–Whitney U-test. Time dependent intragroup data were analysed by Friedman's test. Wilcoxon's rank sum test was used to evaluate the differences within groups toward the first hour values. Bonferroni's correction was applied (P<0.05/n; where n = number of comparisons) when multiple comparisons were made. The incidence of complications between the groups was analysed by using the χ^2-test. Results are presented as mean (95% CI) or (SD), and median (min–max).

Results

There were no differences between groups in patient characteristics (sex, age and weight), type of surgery, number of patients requiring supplementary meperidine and duration of anaesthesia (Table 1). The mean time to extubation at the end of anaesthesia, and time to recovery were significantly longer (P<0.017) in Group M than in Group S (Table 1). There were no statistically significant differences in Sp_{O_2} values between groups, and no great variations or differences in the haemodynamic data. Values remained within the normal range throughout the study period.

Postoperative pain after abdominal surgery was treated successfully in all three groups; no patient needed any change in the analgesic technique or setting of the PCA pump. Repeated analysis (Friedman test) was performed to evaluate the effect of time; time was found to affect VRS, discomfort, and sedation (P<0.05).

Comparing within groups, VRS, discomfort, and sedation scores decreased significantly with time in each group (P<0.01). There were no significant differences between groups in mean pain, discomfort and sedation scores at any study period (Table 2).

Although VRS, discomfort, and sedation scores were similar, cumulative morphine consumption differed significantly between groups. Compared with Group S, patients given pre-emptive morphine consumed 28% less morphine and those given pre-emptive tramadol consumed 17% less morphine in the first 24 h (P<0.017; Table 2). Cumulative morphine consumption was significantly lower in Group M (P<0.017) at both 12 and 24 h after starting the PCA than in Group S. In Group T, it was lower only after 24 h (P<0.017). There were no significant differences in cumulative morphine consumption between Groups T and M (Table 2).

Ten patients (11.1%) (four in Group S (13.3%), three in Group T (10%) and three in Group M (10%)) complained of pain during the first 2 h despite the PCA therapy, and these were treated with i.v. single dose of meperidine (0.4 mg kg^{-1}). There was no significant difference between groups.

Six patients (20%) in Group S, six in Group T (20%) and eight in Group M (26%) experienced nausea despite antiemetic prophylaxis given i.v., and were treated with 4 mg ondansetron IV. The incidence of nausea did not differ significantly between groups, and no patient vomited after PCA therapy.

Discussion

The main finding of this study is that, in patients undergoing major abdominal surgery, pre-emptive treatment with both morphine and tramadol did not result in a perceptible decrease in postoperative pain.

These drugs given before surgery lead to a significantly lower consumption of morphine during the first 24 h. Possible mechanisms include pre-emptive effects, additive effects, or a ceiling effect of the morphine PCA. Studies of pre-emptive analgesia in humans have shown conflicting results. Although some studies of pre-emptive morphine have reported small reductions in analgesic consumption, most have not demonstrated any benefit at all.[12]

In this study, to achieve a clinically relevant pre-emptive effect, tramadol (1 mg kg^{-1}) or morphine (0.1 mg kg^{-1}) was used, although it is perhaps naive to expect that opioids alone could significantly prevent central sensitization.[11] Similar pain scores were reported at each study period, that is, pre-treatment did not sufficiently block afferent input after surgery. The reason for the small or non-existent effect of pre-emptive analgesia might be related to the conditions chosen to demonstrate this effect. At least five potential problems have been reported.[12] These include: the definition of pre-emptive analgesia; the potential pre-emptive analgesic effects of other agents (e.g. opioids, nitrous oxide, and pentobarbital) used routinely as part of the general anaesthetic; the role of post-operative inflammation in initiating and enhancing a state of central sensitization; and the lack of a true placebo control condition. In this study, the non-existent effect of pre-emptive analgesia might be because of its suppression by general anaesthesia. In clinical practice, surgical stimulation always occurs during general anaesthesia, regardless of whether opioids are administered before or after the surgical stimulus. Furthermore, one experimental study demonstrated that halothane antagonized the pre-emptive analgesia produced by nitrous oxide in rats.[13]

Second, the chosen doses of tramadol and morphine may have been inadequate to block afferent input after surgery. Blood concentrations of tramadol or morphine, administrated after induction of anaesthesia, would have been low towards the end of operation, allowing hyperexcitability of the spinal cord, and abolishing any difference between groups. In one study in patients undergoing hysterectomy, a large dose of morphine (0.3 mg kg^{-1}) i.v. on induction of anaesthesia significantly reduced postoperative PCA morphine requirements compared with a dose of 0.15 mg kg^{-1}.[9] However, more recently, it has been demonstrated that preoperative opioids potentiate the analgesic effects of morphine postoperatively even at small doses.[5 9]

On the other hand, the timing of the morphine PCA loading dose might also conceal any pre-emptive effect. As it is reputed to be somewhat slow-acting,[14] morphine was administered at the beginning of closure of the peritoneum. We reasoned that at the end of operation, the drug would exert its maximum effects; this may have abolished any difference between groups.

Aida and colleagues reported that pre-emptive analgesia is effective in limb surgery and mastectomy, but ineffective for gastrectomy, hysterectomy, herniorrhaphy, and appendectomy.[7] In that study, the lack of effect of pre-emptive analgesia in abdominal surgery was related to the different innervations of the abdominal viscera and peritoneum. More recently, however, epidural morphine alone has been shown to exert a significant pre-emptive effect in patients undergoing gastrectomy. Some different pre-emptive effects observed in the current and previous studies may be attributable to differences in the surgical area (the upper abdomen and the extremity) and surgical manipulation. Pain perception during gastrectomy is regulated by multiple mechanisms.[7]

Finally, it may not be possible to demonstrate a pre-emptive effect in a clinical (surgical) setting, as painful stimuli are not confined to the intraoperative period, but extend from hours to days after surgery. Therefore, spinal cord wind-up or central sensitization may occur at any time when analgesia is incomplete.

The additive effects of presurgical treatment may also explain the lower PCA morphine consumption in Groups T and M with similar VRS ratings. Pre-treatment with opioids potentiates the analgesic effects of morphine in post-operative patients.[5 9] Similarly, maximum analgesia occurs 1–2 h after i.v. tramadol administration, and presurgical treatment with tramadol may supplement the analgesic effect of the PCA.[6] These findings may explain the lower PCA morphine consumption in the treatment groups.

According to Woolf and Chong's theory,[15] optimal pre-emptive analgesia not only begins before surgical incision, but also continuously prevents noxious stimuli from over-exciting the nociceptive system, before, during and after surgery. After 12 and 24 h, lower PCA morphine consumption in Groups M and T reflects progressively diminishing effective blood concentrations of morphine. Therefore, although VRS discomfort and sedation scores were similar, our results suggested that presurgical treatment with either tramadol or morphine might have caused a ceiling morphine PCA effect, possibly emerging at 12–24 h. This is similar to, but later in onset than, other reports of the pre-emptive effect of opioids.[16 17]

Opioids have significant side-effects (nausea and vomiting, sedation, respiratory depression, cough suppression, urinary retention, and constipation). They may also delay recovery from anaesthesia and surgery.[18] Recovery times were significantly longer than in Group S, only in Group M ($P<0.017$), but the apparently more rapid recovery from anaesthesia after tramadol compared with morphine did not achieve statistical significance.

In conclusion, in patients who underwent major abdominal surgery, tramadol, administered after induction of anaesthesia at a dose of 1 mg kg^{-1}, led to equivalent postoperative pain relief, similar recovery and postoperative

PCA morphine consumption as morphine 0.1 mg kg^{-1}. These results also suggest that presurgical exposure to systemic opioid analgesia may not result in clinically perceptible benefits.

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