Perioperative antinociceptive effects of tramadol. A prospective, randomized, double-blind comparison with morphine

Mohamed Naguib MB BCH MSC FFARCSI MD,
Mohamed Seraj MB BCH DA FFARCSI,
Mounir Attia MB BCH MSC KSUF AB,
Abdulhamid H. Samarkandi MB BS KSUF FFARCSI,
Mustafa Seet MB BS AB,
Randa Jaroudi RPH*

Purpose: To compare the efficacy of tramadol and morphine for intra- and postoperative analgesia in patients undergoing laparoscopic cholecystectomy.

Methods: In a prospective, randomized, double-blind study 100 patients were allocated randomly into two groups. Ten minutes before induction of anaesthesia, patients in group 1 received 100 mg tramadol and those in group 2 received 10 mg morphine *iv.* Anaesthesia was induced with 5 $mg \cdot kg^{-1}$ thiopental and was maintained with O_2, N_2O plus isoflurane with additional doses of tramadol or morphine as decided by the attending anaesthetist. Postoperatively, patients in group 1 and group 2 received tramadol and morphine, respectively, from a patient-controlled analgesia (PCA) device. Pain, analgesic consumption, vital signs and side effects were recorded postoperatively for 24 hr.

Results: Intraoperative consumption of tramadol and morphine were 137 ± 37 and 12.2 ± 3 mg, respectively. Compared with morphine, patients receiving tramadol had higher blood pressures and required greater mean ET_{iso} to control haemodynamic variables ($P < 0.05$). Postoperatively, there were no differences in observer pain score or visual analogue pain score during the first 24 hr between groups except at 30, 45, and 90 min where patients in the tramadol group reported higher pain scores ($P < 0.05$). The cumulative, 24 hr PCA consumption was 111 ± 93 and 7.5 ± 6.6 mg of tramadol and morphine, respectively.

Conclusions: There was no difference between the use of tramadol and morphine to treat pain after laparoscopic cholecystectomy from 90 min after the end of surgery. Morphine was more effective than tramadol as an intraoperative analgesic.

Objectif : Comparer l'efficacité du tramadol et de la morphine pour l'analgésie peropératoire et postopératoire de patients devant subir une cholécystectomie laparoscopique.

Méthode : Lors d'une étude prospective, randomisée et en double aveugle, 100 patients ont été répartis au hasard en deux groupes. Dix minutes avant l'induction de l'anesthésie, les patients du groupe 1 ont reçu 100 mg de tramadol et ceux du groupe 2, 10 mg de morphine *iv.* L'anesthésie a été induite avec 5 $mg \cdot kg^{-1}$ de thiopental et a été maintenue avec un mélange d'O_2 et de N_2O plus de l'isoflurane et des doses supplémentaires de tramadol ou de morphine selon la décision de l'anesthésiste traitant. Après l'intervention, les patients des groupes 1 et 2 ont reçu respectivement du tramadol et de la morphine à l'aide d'un dispositif d'analgésie contrôlée par le patient (ACP). En période postopératoire également, on a enregistré pendant 24 heures la douleur, la consommation d'analgésiques, les signes vitaux et les effets secondaires.

Résultats : La consommation peropératoire de tramadol et de morphine a été de 137 ± 37 et de 12,2 ± 3 mg, respectivement. Comparativement, les patients qui ont reçu du tramadol ont présenté une tension artérielle plus élevée et ont eu besoin d'$isoflurane_{TE}$ (télé-expiratoire) de moyenne plus élevée pour contrôler les variables hémodynamiques $P < 0,05$). Il n'y a pas eu de différence de douleur postopératoire entre les groupes d'après les niveaux enregistrés par un observateur ou par l'échelle visuelle analogique, pendant les 24 premières heures, sauf à 30, 45 et 90 min alors que les patients du groupe ayant reçu du tramadol ont éprouvé des douleurs plus intenses ($P < 0,05$). La consommation totale des 24 h d'ACP a été de 111 ± 93 et de 7,5 ± 6,6 mg de tramadol et de morphine, respectivement.

Conclusion : À partir de 90 min après la chirurgie, il n'y a pas de différence entre l'usage de tramadol ou de morphine pour traiter la douleur consécutive à la cholécystectomie laparoscopique. La morphine a été plus efficace que le tramadol en tant qu'analgésique peropératoire.

From the Departments of Anaesthesia and Pharmacy,* King Saud University, College of Medicine at King Khalid University Hospital.
Address correspondence to: Dr. Mohamed Naguib, College of Medicine, Department of Anaesthesia, King Khalid University Hospital, PO Box 7805, Riyadh 11472 Saudi Arabia. Phone: 9661-467-1578/467-1597; Fax: 9661-467-9364; E-mail: naguib01@ksu.edu.sa
Presented at the ASA meeting, October 17-21, 1998, Orlando, Florida. This study was supported by Grünenthal GmbH.
Accepted for publication September 25, 1998

TRAMADOL hydrochloride is a synthetic mu-opioid agonist with additional monoaminergic activity through the inhibition of the neuronal uptake of serotonin and norepinephrine.[1] Its intravenous analgesic effect has been reported to be 10 times less than that of morphine,[2] with a more favourable side effect profile.[3] Unlike typical opioid analgesics, the therapeutic use of tramadol has not been associated with the clinically important side effects such as respiratory depression, constipation or sedation. In addition, analgesic tolerance has not been a serious problem during repeated administration, and neither psychological dependence nor euphoric effects are observed in long-term clinical trials.[4] Although several studies have documented the efficacy of tramadol for treating pain after different surgical procedures,[3–7] none has looked at its efficacy as an intraoperative analgesic in comparison with traditional opioids. It has been suggested that tramadol is unsuitable for intraoperative use because of the fear of intraoperative lightening of anaesthesia, when tramadol is used as a part of (and not added to) an anaesthetic regimen.[8] This concern, however, has not been substantiated in recent studies.[9,10]

Tramadol-induced antinociception has never been compared with that of morphine in the perioperative period. This prospective, randomized, double-blind study looked at the efficacy of tramadol as an intraoperative analgesic in comparison with morphine and compared the postoperative analgesic effects of both drugs in patients who underwent laparoscopic cholecystectomy.

Patients and methods

After obtaining informed consent and approval from the local Ethics Committee, we studied 100 ASA group I or II patients of both sexes, aged 18-51 (mean 33 ± 7.6) yr and weighing 41-97 (mean 70.5 ± 10.4) kg. All patients were undergoing elective laparoscopic cholecystectomy. At the pre-anaesthesia visit, the patient was instructed in the use of the visual analogue pain scale, the patient-controlled analgesia (PCA) machine (Abbott Pain Management Provider). Inability of the patient to comply with the requirements of the study was grounds for exclusion. None of the patients was pregnant or lactating, abusing centrally acting drugs, consuming monoamine oxidase inhibitors, or allergic to study drugs. Lorazepam 2 mg *po* was given as premedication 90 min preoperatively.

Part 1: Intraoperative Analgesia

In the operating room, a 20-G radial arterial cannula was inserted under local anaesthesia before induction of general anaesthesia. Electrocardiogram, and direct arterial pressure were monitored continuously using HP M1166 A, Model 68 S, with write-out capability in the event of need for documentation of possible rhythm disturbances. Hemoglobin O_2 saturation was monitored by pulse oximetry. Temperature was monitored by a nasopharyngeal thermistor and was maintained at 36.5 ± 0.5°C. Neuromuscular function was monitored by a peripheral nerve stimulator.

Patients were randomly allocated into two groups (n = 50 in each), to receive either tramadol or morphine for intra- and postoperative analgesia. The same drug was administered for both intra- and postoperative courses. For intraoperative use, study drugs were prepared by a pharmacist in two 10 ml syringes (containing either 100 mg tramadol or 10 mg morphine per syringe) and marked only with a coded label to maintain the double-blind nature of the study. Ten minutes before induction of anaesthesia, patients in group 1 received 100 mg tramadol and those in group 2 received 10 mg morphine *iv* (the contents of a 10 ml syringe). Ondansetron 4 mg *iv* was administered to all patients. A standard anaesthetic technique was used in all patients. Anaesthesia was induced with 5 $mg \cdot kg^{-1}$ thiopental and was maintained with nitrous oxide 70% and isoflurane in oxygen 30%. Tracheal intubation was facilitated with 0.5 $mg \cdot kg^{-1}$ atracurium. After tracheal intubation, an orogastric tube was inserted in all patients to ensure baseline emptying of the stomach of air and gastric contents. The concentrations of nitrous oxide, oxygen, carbon dioxide and isoflurane were determined continuously by a multiple-gas anaesthesia monitor (Datex-Engstrom-Capnomac Ultima). Ventilation was adjusted to maintain normocapnia ($P_{ET}CO_2$ 35-40 mmHg). Increasing the inspired isoflurane concentration and/or administration of additional analgesia (coded drugs) using incremental doses of tramadol in group 1 or morphine in group 2 were allowed from the second 10 ml syringe (as decided by the attending anaesthetist) whenever heart rate or systolic blood pressure increased > 20% of its control value. The maximum dose allowed for intraoperative use was 200 mg tramadol or 20 mg morphine. No opioids were administered intraoperatively except for the tramadol or morphine as per the study protocol. At the end of anaesthesia, residual neuromuscular blockade was antagonized with 0.05 $mg \cdot kg^{-1}$ neostigmine and 0.02 $mg \cdot kg^{-1}$ atropine. The nasogastric tube was removed in the operating room.

Part 2: Postoperative Analgesia

Patients in group 1 and group 2 received tramadol and morphine, respectively, from a PCA device for

postoperative analgesia. The two study drugs were identically packaged and contained equipotent doses of each drug (100 ml containing 400 mg tramadol or 40 mg morphine) and were coded by the pharmacist to maintain the double-blind nature of the study during the postoperative course. The PCA parameters were: 1. No background infusion; 2. Demand dose - 4 ml (16 mg tramadol or 1.6 mg morphine); lockout time - 5 min; four hour limit - 100 ml (400 mg tramadol or 40 mg morphine).

All patients were observed for two hours in the recovery room before returning to the ward. Heart rate and pulse oximetry were monitored continuously and blood pressure was monitored every five minutes by an electronic oscillometer. When the patient was alert in the recovery room, objective pain assessments, respiratory rate, blood pressure, heart rate, side effects (such as nausea, vomiting, dizziness, sedation, dry mouth, sweating, headache were checked from a check list), PCA demand and PCA consumption were recorded. Assessments were made at 15 min intervals for the first hour, 30 min intervals for the second hour and at 3, 4, 5, 6, and 24 hr after recovery from anaesthesia. Pain intensity was assessed on each occasion using a four-point scale (0 = no pain or asleep; 1 = slight pain; 2 = moderate pain; 3 = severe pain). The patient was asked to assess his own pain using a visual analog score along a 10 cm line marked from "no pain" to "most severe pain imaginable". The cumulative PCA consumption in 24 hr was also recorded. Nausea and/or vomiting were treated with 10 mg metoclopramide *iv.* All observations were recorded by one anaesthetist who had been instructed in the study design and score system and who was unaware of the patients' group assignments. The possibility of explicit recall of intraoperative events was assessed on the first postoperative day by asking patients to describe the last thing they remembered before going to sleep, the first item they recalled upon awakening after the operation, and whether or not they recalled any event in between.

Statistical analysis

All statistical analyses were carried out using BMDP statistical package, release 7.01 (University of California Press, Berkeley, California, 1994). An unbalanced repeated measures analysis of variance (ANOVA) was performed to detect changes over time in haemodynamic variables for the two groups (within group comparison). When statistically significant changes were found by ANOVA, Bonferroni adjusted paired t test was performed. Differences between groups were analyzed with unpaired Student's t test.

TABLE I Patients' characteristics (mean ± SD or (range)).

	Tramadol (n = 50)	*Morphine (n = 50)*
Age (yr)	32.6 (18-51)	33.5 (20-48)
Weight (kg)	69.5 ± 11.9	71.4 ± 8.6
Height (cm)	159.9 ± 6.4	160 ± 6
Sex (M/F)	7/43	9/41
Surgical time (min)	85.3 ± 18.1	86.3 ± 18.8

TABLE II Incidence of side effects (% of patients).

	Tramadol (n = 50)	*Morphine (n = 50)*
Nausea	9 (18)	8 (16)
Vomiting	16 (32)	16 (32)
Dry mouth	1 (2)	5 (10)
Restlessness	1 (2)	1 (2)
Tachycardia	3 (6)	2 (4)
Hypertension	1 (2)	0
Tachypnea	1 (2)	0
Drowsiness	3 (6)	2 (4)

The categorical data (pain score, sex distribution and the incidence of side effects) were analyzed with the use of Kruskall-Wallis test, Mann-Whitney test or Fisher's Exact test as appropriate. The times at which first PCA demand was requested were treated as being analogous to survival data. "Survival" curves were plotted to indicate the proportion of patients in each group who had received no analgesia by a given time after operation. These times were compared using Mantel-Cox nonparametric log-rank test. Results were expressed as means and SD and were considered significant when $P < 0.05$.

Results

The groups were comparable with respect to patient characteristics and duration of surgery (Table I).

Part 1: Intraoperative Analgesia

The volumes of morphine and tramadol administered intraoperatively were prepared in equipotent doses as expressed by the ml of administered drug. Each ml contains either 10 mg tramadol or 1 mg morphine based upon the quoted 10:1 potency ratio. Generally, the analgesic requirements during operation were similar in both groups (as expressed by ml of equipotent doses). Nevertheless, there were greater volumes of analgesia administered 10 and 30 min after induction of anaesthesia in the tramadol group than in the morphine group ($P < 0.01$) (Figure 1A). Patients in the morphine

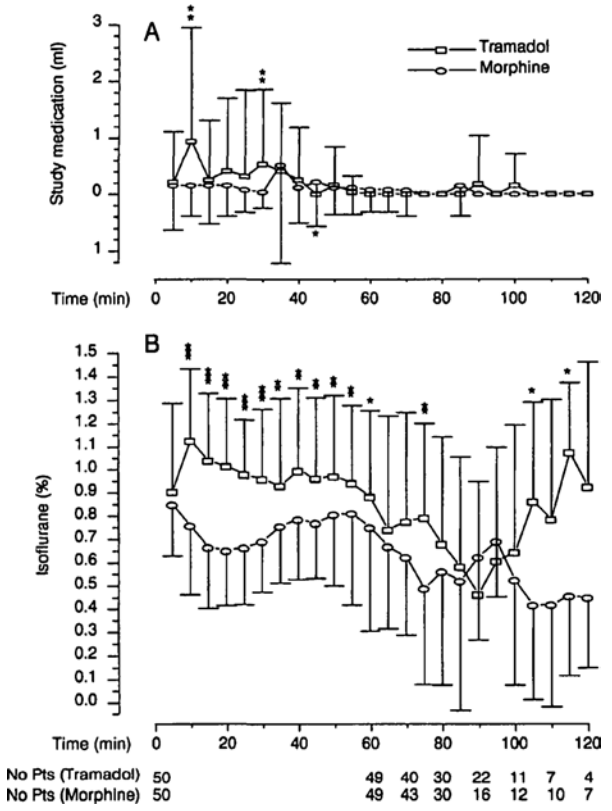

FIGURE 1A. Volumes of tramadol and morphine administered intraoperatively (mean ± SD). Each ml contains either 10 mg tramadol or 1 mg morphine (equipotent doses) assuming that morphine is 10 times more potent than tramadol. **= $P < 0.01$, * = $P < 0.05$. Time 0 = Immediately before induction of anaesthesia.

FIGURE 1B. Intraoperative end-tidal isoflurane (%) in tramadol and morphine groups (mean ± SD). **= $P < 0.01$, * = $P < 0.05$. Time 0 = Immediately before induction of anaesthesia.

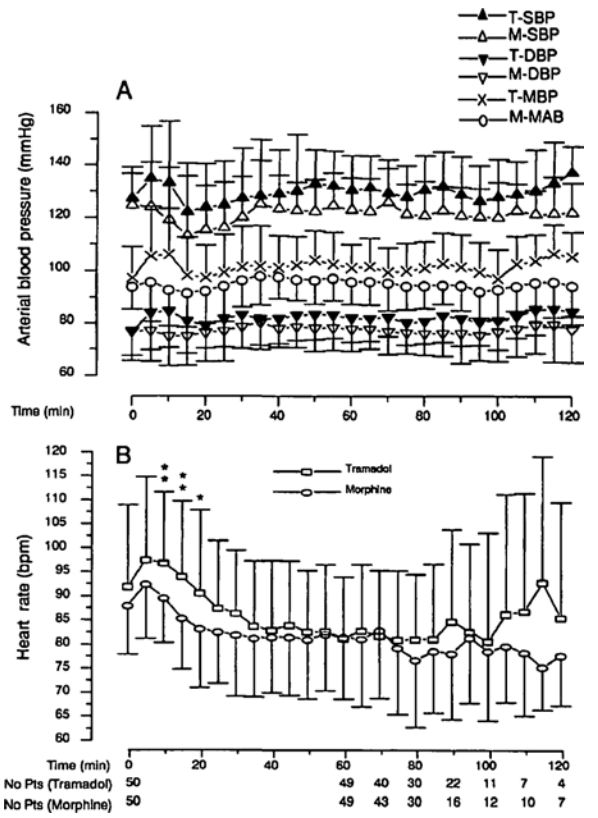

FIGURE 2 (A, B). The time course of intraoperative cardiovascular variables in tramadol (T) and morphine (M) groups (mean and SD). SBP = systolic blood pressure, DBP = diastolic blood pressure, MBP = mean blood pressure. Time 0 = Immediately before induction of anaesthesia.

group needed a larger volume only at 45 min after induction of anaesthesia (Figure 1A). Cumulative doses (including the initial boluses) of tramadol and morphine administered intraoperatively were 137 ± 37 and 12.2 ± 3 mg, respectively. Compared with the morphine group, patients in the tramadol group required a higher mean ET_{iso} in order to control haemodynamic variables ($P < 0.05$) [0.7 ± 0.08% *vs* 1.2 ± 0.2% respectively] (Figure 1B). Haemodynamic data are displayed in figures 2A and 2B. Analysis of variance for repeated measures indicated that the blood pressure pattern for tramadol and morphine groups differed ($P < 0.01$). Patients in tramadol group had a higher blood pressure ($P = 0.0042$) than those in morphine group. No differences were noted in heart rate or oxygen saturation between the groups. Within each group, haemodynamic variables differed over time ($P < 0.005$).

Part 2: Postoperative Analgesia

The volumes of morphine and tramadol administered postoperatively were prepared in equipotent doses as expressed by ml of administered drug. Each ml contained either 4 mg tramadol or 0.4 mg morphine. Postoperative analgesia was achieved in patients in both groups. The number of demands made by patients on the PCA pump was not different between groups except at 90 min where patients in the tramadol group requested more analgesia ($P = 0.03$) (Figure 3A). Likewise, the PCA drug consumption (as expressed in ml of equipotent doses) was greater in the tramadol group at 90 min and at four hours postoperatively ($P < 0.05$) (Figure 3B). The cumulative PCA consumption in 24 hr was 111 ± 93 and 7.5 ± 6.6 mg of tramadol and morphine, respectively (Figure 3C). Time to first postoperative PCA analgesic demand and the proportion of patients requiring no analgesia were not different between the two groups (Figure 3D). There were

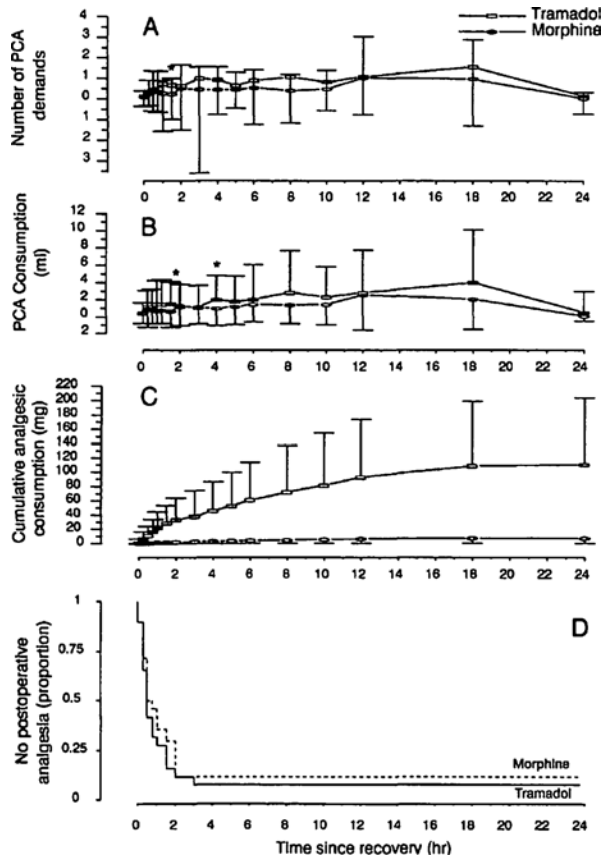

FIGURE 3A. The number of demands made by patients on the PCA pump (mean and SD) at different times postoperatively. * = $P < 0.05$.

FIGURE 3B. PCA drug consumption (mean and SD). The volumes of morphine and tramadol administered postoperatively were prepared in equipotent doses as expressed by ml of administered drug. Each ml contains either 4 mg tramadol or 0.4 mg morphine assuming that morphine is 10 times more potent than tramadol. * = $P < 0.05$.

FIGURE 3C. Mean cumulative PCA consumption (SD) as a function of time in the postoperative period.

FIGURE 3D. Log rank test. Proportion of patients not requesting PCA analgesia. The graph steps down when patients requested analgesia.

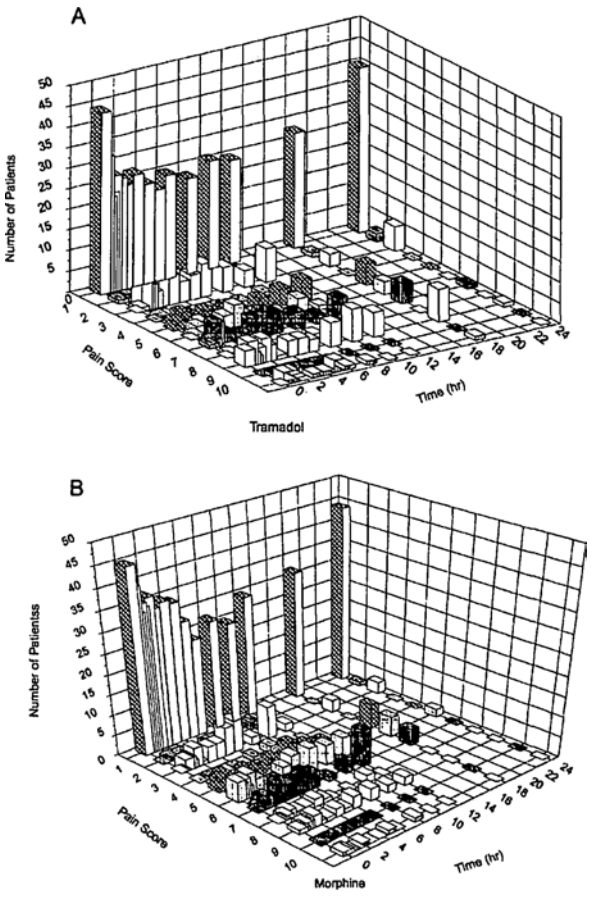

FIGURE 4. Visual analogue pain score in tramadol group (Figure 4A) and morphine group (Figure 4B) during the first 24 hr after surgery. At 30, 45, and 90 min postoperatively, patients in tramadol group reported higher pain score ($P < 0.05$).

no differences in visual analogue pain scores during the first 24 hr postoperatively between the groups except at 30, 45, and 90 min where patients in the tramadol group reported higher pain scores ($P < 0.05$) (Figures 4A, 4B). Observer pain score was not different between the two groups (Figures 5A, 5B) although at four hours postoperatively there was a trend of a higher score in the tramadol group ($P = 0.059$).

The incidence of side effects (Table II) was similar in both groups (P = NS). There were no episodes of recall of intraoperative events. There were no differences in any measured haemodynamic variable when comparing tramadol and morphine postoperative observation periods.

Discussion

This is the first study that compared the efficacy of tramadol-induced antinociceptive activity- in a double-blind manner- with that of morphine during both intra- and postoperative periods. The results demonstrated that patients given tramadol required a greater volume of analgesic solution (at 10 and 30 min) intraoperatively, had higher blood pressures and required higher end-tidal isoflurane concentrations. Despite access to 1.6 mg morphine or 16 mg tramadol at five

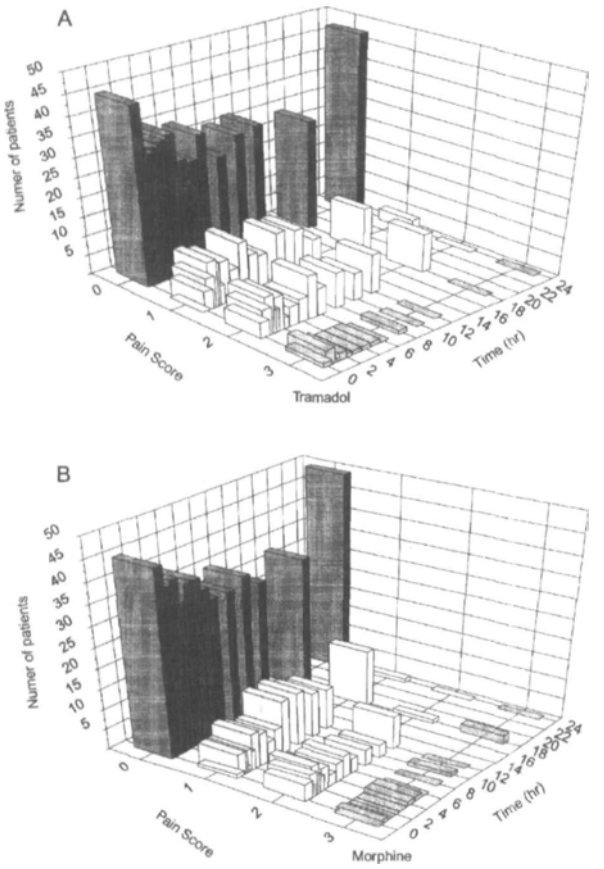

FIGURE 5. Observer pain score in tramadol group (Figure 5A) and morphine group (Figure 5B) during the first 24 hr after surgery (P = NS).

minutes intervals, visual analogue scores in the tramadol group were higher at 30, 45 and 90 min after surgery. However, there was no difference between the use of tramadol and morphine to treat pain after laparoscopic cholecystectomy from 90 min after the end of surgery.

Part 1: Intraoperative Analgesia

Tramadol has been used intraoperatively as part of balanced anaesthesia. However, it has been suggested that tramadol is unsuitable for intraoperative use because 65% of patients reported awareness of music played in the operating room when anaesthesia was administered with tramadol infusion and nitrous oxide, supplemented by intermittent inhalation of low concentrations of enflurane.[8] This suggestion has been disputed in recent studies.[9,10] Tramadol, in doses up to 200 mg *iv* given to adults during stable, light isoflurane-nitrous oxide anaesthesia, did not lead to clinically important lightening of anaesthesia as measured by electroencephalographic changes, incidence of recall, and movement on skin incision.[9] Others have also demonstrated that intravenous bolus administration of 1.5 mg·kg^{-1} tramadol at the time of anaesthesia induction was a complement to general anaesthesia and provided intraoperative analgesia in surgical patients.[10] Although our study was not designed primarily to investigate the incidence of intraoperative recall, in accordance with other investigators,[9] we did not find any evidence of intraoperative conscious recall, either spontaneously or on enquiry. It should be pointed out, however, that we used lorazepam for premedication of our patients and this may have caused amnesia for episodes of intraoperative awareness if the latter had occurred.

Tramadol is not a classical weak opioid but its analgesic effect is probably also mediated through α_2-agonist and serotoninergic activity, which it exerts by inhibiting the re-uptake of noradrenaline and 5-hydroxytryptamine in the central nervous system.[1,11] In this study, greater volumes of analgesia were administered 10 and 30 min after induction of anaesthesia in the tramadol group than in the morphine group ($P < 0.01$) (Figure 1A). The cumulative doses of tramadol and morphine administered intraoperatively were 137 ± 37 and 12.2 ± 3 mg, respectively (an equipotency of 1:11, respectively). Further, there were differences in measured haemodynamic variables when comparing tramadol and morphine intraoperative observation periods. Patients in the tramadol group had a higher blood pressure ($P = 0.0042$) than those in morphine group (Figure 2). This resulted in administration of higher ($P < 0.05$) isoflurane concentrations to patients in the tramadol group in order to control haemodynamic variables (Figure 1B). It has been shown that peritoneal CO_2 insufflation to an intraabdominal pressure of 14 mm Hg, necessary for laparoscopic cholecystectomy, resulted in major haemodynamic changes in healthy non-obese patients without cardiac disease. These disturbances were characterized by an increase in mean arterial pressure, systemic vascular resistance, and pulmonary vascular resistance, and a decrease of cardiac index. Cardia index markedly decreased to as much as 50% of preoperative values five minutes after the beginning of insufflation.[12]

Part 2: Postoperative Analgesia

Laparoscopic cholecystectomy is associated with less deterioration in postoperative pulmonary function,[13] and lower morbidity and mortality rates[14] than in the traditional open cholecystectomy. Nevertheless, a considerable proportion of patients complain of pain in the

postoperative period following laparoscopic cholecystectomy and may require substantial amounts of opioids to gain relief.[15] Patients may complain of visceral and shoulder pain more than abdominal wall (parietal) pain after laparoscopic cholecystectomy.[16] Therefore, laparoscopic cholecystectomy might represent an interesting model to investigate visceral pain and its relief by different analgesic drugs in humans.[16] A recent study by Rademaker *et al.*[13] did not support the contention of decreased opioid requirements and lower pain scores in laparoscopic cholecystectomy than in open cholecystectomy patients. The authors noted that pain scores did not differ at any time in the first 24 hr after surgery and the requirements for opioids in the first 24 hr were similar.[13] In another study, the degree of pain until the first postoperative morning has been shown to be strong or even unbearable in about half of the patients after laparoscopic cholecystectomy.[17] It has been reported that mean cumulative PCA demands and PCA morphine consumption in the first four hours after laparoscopic cholecystectomy were 50 and 10.4 mg, respectively.[18] Pain after laparoscopy has been reviewed recently by Alexander.[19]

Lehmann *et al.*[4] reported that the average PCA tramadol consumption (after a loading dose of 97.5 ± 42.3 mg) was 160 ± 99.5 mg over 20.5 ± 4.8 hr in patients recovering from major orthopaedic or gynaecological operations. In this study, the cumulative PCA consumption in 24 hr was 111 ± 93 and 7.5 ± 6.6 mg of tramadol and morphine, respectively. It appears, therefore, that tramadol is approximately 1/15 as potent as morphine. Published data support a 1:10 to 1:15 morphine/tramadol efficacy ratio.[3,4,20] Further, we noted in this study that observer pain score, time to first postoperative PCA analgesic demand and the number of demands were not different between groups (except at 90 min where patients in tramadol group requested more analgesia). The percentage of patients requiring no postoperative analgesia was similar for the two groups (P = NS). Six patients (12%) in the morphine group and 4 patients (8%) in the tramadol group required no analgesia in the postoperative course (Figure 3D). There were no differences in visual analogue pain score during the first 24 hr postoperatively between the groups except at 30, 45, and 90 min where patients in tramadol group reported higher pain scores ($P < 0.05$).

Baraka *et al.*[21] reported that epidural tramadol (100 mg) provided adequate and prolonged postoperative analgesia similar to that produced by epidural morphine (4 mg) in patients undergoing major abdominal surgery without respiratory depression. In contrast, the mean PaO_2 in patients who received epidural morphine was decreased from the sixth hour postoperatively.[21] Previous clinical reports have also shown that parenteral morphine resulted in greater, and clinically important, respiratory depression than equi-analgesic doses of parenteral tramadol.[3,22]

Naguib *et al.*[23] reported that the incidence of postoperative nausea and vomiting (PONV) after laparoscopic cholecystectomy was 72.4% which was reduced to 34.5% after prophylactic administration of 4 mg ondansetron. In the current study, all patients received 4 mg ondansetron before induction of anaesthesia. A comparable incidence was noted in this study (Table II). The side effects noted in this study were mostly of minor intensity and were comparable in both groups (Table II).

In conclusion, this study demonstrated that there was no difference between the use of tramadol and morphine to treat pain after laparoscopic cholecystectomy from 90 min after the end of surgery. Morphine was more effective than tramadol as an intraoperative analgesic.

References

1 *Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL.* Opioid and non-opioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. J Pharmacol Exp Ther 1992; 260: 275–85.

2 *Hennies H-H, Friderichs E, Schneider J.* Receptor binding, analgesic and antitussive potency of tramadol and other selected opioids. Arzneimittelforschung 1988; 38: 877–80.

3 *Houmes R-JM, Voets MA, Verkaaik A, Erdmann W, Lachmann B.* Efficacy and safety of tramadol versus morphine for moderate and severe postoperative pain with special regard to respiratory depression. Anesth Analg 1992; 74: 510–4.

4 *Lehmann KA, Kratzenberg U, Schroeder-Bark B, Horrichs-Haermeyer G.* Postoperative patient- controlled analgesia with tramadol: analgesic efficacy and minimum effective concentrations. Clin J Pain 1990; 6: 212–20.

5 *Kupers R, Callebaut V, Debois V, et al.* Efficacy and safety of oral tramadol and pentazocine for postoperative pain following prolapsed intervertebral disc repair. Acta Anæsthesiol Belg 1995; 46: 31–7.

6 *James MFM, Heijke SAM, Gordon PC.* Intravenous tramadol versus epidural morphine for postthoracotomy pain relief: a placebo-controlled double-blind study. Anesth Analg 1996; 83: 87–91.

7 *Ng KFJ, Tsui SL, Yang JCS, Ho ETF.* Comparison of tramadol and tramadol/droperidol mixture for patient-controlled analgesia. Can J Anaesth 1997; 44: 810–5.

8 *Lehmann KA, Horrichs G, Hoeckle W.* Tramadol as an intraoperative analgesic. A randomised double- blind study with placebo. Anaesthesist 1985; 34: 11–9.

9 *Coetzee JF, Maritz JS, Du Toit JC.* Effect of tramadol on depth of anaesthesia. Br J Anaesth 1996; 76: 415–8.
10 *Lauretti GR, Mattos AL, Lima IC.* Tramadol and beta-cyclodextrin piroxicam. Effective multimodal balanced analgesia for the intra- and postoperative period. Reg Anesth 1997; 22: 243–8.
11 *Desmeules JA, Piguet V, Collart L, Dayer P.* Contribution of monoaminergic modulation to the analgesic effect of tramadol. Br J Clin Pharmacol 1996; 41: 7–12.
12 *Joris JL, Noirot DP, Legrand MJ, Jacquet NJ, Lamy ML.* Hemodynamic changes during laparoscopic cholecystectomy. Anesth Analg 1993; 76: 1067–71.
13 *Rademaker BM, Ringers J, Odoom JA, de Wit LT, Kalkman CJ, Oosting J.* Pulmonary function and stress response after laparoscopic cholecystectomy: comparison with subcostal incision and influence of thoracic epidural analgesia. Anesth Analg 1992; 75: 381–5.
14 *Holohan TV.* Laparoscopic cholecystectomy. Lancet 1991; 338: 801–3.
15 *Rose DK, Cohen MM, Soutter DI.* Laparoscopic cholecystectomy: the anaesthetist's point of view. Can J Anaesth 1992; 39: 809–15.
16 *Joris J, Thiry E, Paris P, Weerts J, Lamy M.* Pain after laparoscopic cholecystectomy: characteristics and effect of intraperitoneal bupivacaine. Anesth Analg 1995; 81: 379–84.
17 *Scheinin B, Kellokumpu I, Lindgren L, Haglund C, Rosenberg PH.* Effect of intraperitoneal bupivacaine on pain after laparoscopic cholecystectomy. Acta Anaesthesiol Scand 1995; 39: 195–8.
18 *Fredman B, Jedeikin R, Olsfanger D, Flor P, Gruzman A.* Residual pneumoperitoneum: a cause of postoperative pain after laparoscopic cholecystectomy. Anesth Analg 1994; 79: 152–4.
19 *Alexander JI.* Pain after laparoscopy. Br J Anaesth 1997; 79: 369–78.
20 *Vickers MD, Paravicini D.* Comparison of tramadol with morphine for post-operative pain following abdominal surgery. Eur J Anaesthesiol 1995; 12: 265–71.
21 *Baraka A, Jabbour S, Ghabash M, Nader A, Khoury G, Sibai A.* A comparison of epidural tramadol and epidural morphine for postoperative analgesia. Can J Anaesth 1993; 40: 308–13.
22 *Vickers MD, O'Flaherty D, Szekely SM, Read M, Yoshizumi J.* Tramadol: pain relief by an opioid without depression of respiration. Anaesthesia 1992; 47: 291–6.
23 *Naguib M, El Bakry AK, Khoshim MHB, et al.* Prophylactic antiemetic therapy with ondansetron, tropisetron, granisetron and metoclopramide in patients undergoing laparoscopic cholecystectomy: a randomized, double-blind comparison with placebo. Can J Anaesth 1996; 43: 226–31.