Comparison of patient-controlled analgesia (PCA) with tramadol or morphine

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Purpose: To compared the clinical efficacy of tramadol and morphine using a patient-controlled analgesia (PCA) delivery system.

Methods: In a prospective, randomized, double blind study, we evaluated 80 adult patients scheduled for elective hip or knee arthroplasty with general inhalational anesthesia. When patients complained of pain in the recovery room, patients were randomized to receive either tramadol or morphine by titration in 30 min to achieve analgesia (VAS ≤ 4). Equivalent volumes containing either 30 $mg \cdot ml^{-1}$ tramadol or 1 $mg \cdot ml^{-1}$ morphine were used for PCA with a lockout interval of 10 min. The patients were followed six-hourly for 48 hr for VAS, satisfaction rate, analgesic dose, and side effects.

Results: Patients obtained adequate analgesia with either drug. More patients had very good satisfaction scores in the morphine group in the recovery room (43% *vs* 23%, $P < 0.05$) and at 24 hr (40% *vs* 20%, $P < 0.05$) than those in the tramadol group. More nausea was evident in the tramadol group (48% *vs* 11% in recovery room and 28% *vs* 12% in 24 hr, $P < 0.05$) than in the morphine group. Vomiting was also more (28% *vs* 5% in recovery room, 15% *vs* 3% in 24 hr, $P < 0.05$). Morphine produced more sleepiness (45% *vs* 23% in recovery room, $P < 0.05$ and 35% *vs* 15% in 24 hr, $P < 0.05$).

Conclusion: Tramadol PCA can provide effective analgesia following major orthopedic surgery provided sufficiently high doses are given for loading and by patient demand. However, the incidence of nausea/vomiting is also higher causing decreased satisfaction.

Objectif : Comparer l'efficacité clinique du tramadol et de la morphine en utilisant un système d'analgésie contrôlée par le patient (ACP).

Méthode : Lors d'une étude prospective, randomisée et en double aveugle, nous avons évalué 80 adultes dont l'arthroplastie de la hanche ou du genou avait été prévue avec une anesthésie générale d'inhalation. À la salle de réveil, les patients répartis au hasard ont reçu, quand ils éprouvaient de la douleur, du tramadol ou de la morphine selon un dosage permettant d'atteindre l'analgésie (EVA ≤ 4) en 30 min. Des volumes équivalents contenant 30 $mg \cdot ml^{-1}$ de tramadol ou 1 $mg \cdot ml^{-1}$ de morphine ont été utilisés pour l'ACP, qui comprenait une période réfractaire de 10 min. Les patients ont été revus à toutes les six heures pendant 48 h pour l'enregistrement des scores de l'EVA, de la satisfaction, de la dose d'analgésique et des effets secondaires.

Résultats : Les patients ont obtenu une analgésie suffisante avec l'un ou l'autre médicament. Un plus grand nombre de patients a été très satisfait dans le groupe ayant reçu de la morphine à la salle de réveil (43 % *vs* 23 %, $P < 0,05$) et à 24 h (40 % *vs* 20 %, $P < 0,05$) que ceux du groupe ayant reçu le tramadol. Il y a eu davantage de nausées dans le groupe du tramadol (48 % *vs* 11 % dans la salle de réveil et 28 % *vs* 12 % à pendant les 24 premières heures, $P < 0,05$) que dans le groupe de la morphine. Les vomissements ont été également plus fréquents (28 % *vs* 5 % en salle de réveil, 15 % *vs* 3 % pendant les 24 premières heures, $P < 0,05$). La morphine a produit plus de somnolence (45 % *vs* 23 % en salle de réveil, $P < 0,05$ et 35 % *vs* 15 % pendant 24 h, $P < 0,05$).

Conclusion : L'ACP avec le tramadol peut assurer une analgésie efficace à la suite d'une intervention orthopédique importante, pourvu que des doses suffisamment élevées soient administrées en dose d'attaque et à la demande du patient. Cependant, l'incidence de nausées et de vomissements est aussi plus élevée avec le tramadol, ce qui en diminue l'attrait.

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VARIOUS attempts have been made to improve pain relief after major surgery. The most commonly used drug for intravenous (*iv*) patient controlled analgesia (PCA) is morphine, an opioid that has several adverse effects.

Tramadol is a centrally acting analgesic with both opioid and non-opioid modes of action.[1,2] It is effective for the relief of acute and chronic pain.[3,4] The adverse effect profile of tramadol, especially respiratory depression, is that of a weak opioid at effective analgesic doses.[5] With low abuse and addiction potential,[6] tramadol is not a controlled substance in many countries. However, only one article was found in the English literature in which the analgesic and side effect profiles of PCA tramadol were compared with those of morphine.[7] They concluded that effective postoperative analgesia can be achieved by either PCA morphine or tramadol and the side effects, especially nausea and vomiting were also comparable.[7] However, in that study only responders to loading doses (up to 200 mg tramadol or 20 mg morphine) in 30 min were recruited for further comparison and all the patients received 2.5 mg droperidol and 10 mg metoclopramide during surgery.[7] We undertook the present study without this exclusion or the use of intraoperative anti-emetics to re-evaluate the comparative clinical efficacy of tramadol PCA with that of morphine with a less restricted protocol.

Methods

Following approval of the hospital Research Committee and informed consent, 80 adult patients were enrolled in this prospective, randomized, double blind study. Patients who underwent either total hip or total knee arthroplasty were studied. All patients were instructed in the use of the PCA device during the preoperative interview and again in the recovery room. Exclusion criteria included: (1) allergy to the study drugs, (2) inability to use PCA, (3) difficulty in communication (4) history of hepatic, cardiopulmonary or renal disease (5) history of substance abuse. Anesthesia was induced with 4 $mg \cdot kg^{-1}$ thiopental and 1 $mg \cdot kg^{-1}$ succinylcholine *iv* and maintained with nitrous oxide 60%/isoflurane 1-3%. No opioids, local anesthetics, anti-emetics or non-steroidal anti-inflammatory drugs were administered 24 hr before or during surgery. After surgery and as soon as the patient complained of pain in the recovery room, a baseline pain assessment was done with a Visual Analog Pain Score (VAS) with 0 being no pain and 10 being the most excruciating pain. The patient was then randomly assigned to receive incremental doses of either tramadol (Tramtor®, Patron Chemical & Pharmaceutical Co., Taiwan) or morphine (Ministry of Health, Taiwan) over 30 min until VAS $\leq$ 4 was achieved as assessed by an anesthesiologist blinded to the identity of the drug. Similar syringes of either 30 $mg \cdot ml^{-1}$ tramadol or 1 $mg \cdot ml^{-1}$ morphine in equal volumes prepared by a pharmacist were used for the loading dose. Then, the patient was connected to a PCA pump (Lifecare Infusor-4200 Abbott Laboratories, North Chicago, USA.) with the same concentration of either drug (30 $mg \cdot ml^{-1}$ tramadol or 1 $mg \cdot ml^{-1}$ morphine). The PCA pump was set to deliver bolus doses of 1 ml with a lockout interval of 10 min. No background infusion or four-hour maximal limit was set. In either group, rescue analgesia with titration of 25-50 mg meperidine *iv* was allowed if the patient could not obtain adequate pain relief from the above PCA regimen.

An anesthesia resident blinded to the identity of the drug carried out the pain assessment every six hours for 48 hr. At interview, the patient was instructed to inform the investigator of the overall pain relief at rest for the past six hours using the visual analogue scale (VAS). Patients were also asked to express their satisfaction of their pain control in the recovery room and every 24 hr with a Global Satisfaction Score which was divided into "very good," "good" "fair," and "poor".

Data on dosing patterns, demand, delivery and total accumulated dose (total loading dose was not included) were retrieved from the PCA computer memory. Vital signs (blood pressure, heart rate, respiratory rate), side effects and rescue medications were recorded throughout the 48-hr observation period.

All adverse events were recorded. Respiratory depression was defined as a respiratory rate <10 $breath \cdot min^{-1}$ or unrousable sleep and was treated by termination of PCA and naloxone *iv* as required. Metoclopramide, 10 mg *iv* four-hourly, was given for persistent nausea and/or if there were two episodes of consecutive vomiting. Urinary retention could not be assessed due to the use of indwelling catheters in all the patients. Pruritus was treated with 5 mg diphenhydramine *iv* if needed. The degree of sedation was rated on a four-point scale: 0 = awake, 1 = sleepy, 2 = somnolent but responded to verbal command or pain stimulation, 3 = unrousable. A sedation score of scale 3 would be treated as for respiratory depression.

Data for age, body weight, and height were analyzed with Student's t test and reported as mean ± SD. The VAS was analyzed with Mann Whitney U test. A Chi-square test was used for sex, types of surgery and satisfaction score. Chi-square test and Fisher's exact test were used for the analysis of adverse effects. A P value < 0.05 was considered statistically significant.

Results

There were no differences between the two groups in terms of age, sex, weight, height, and type of surgery (Table I).

The onset of both tramadol or morphine was about five minutes, and VAS ≤ 4 in the recovery room was achieved in 30 min in both groups. The pain scores in the recovery room and at 6, 12, 18, 24, 30, 36, 42 and 48 hr interviews were similar (Figure). The total loading doses in the recovery room were 284.9 ± 156.6 mg for tramadol and 13.1 ± 4.4 mg for morphine. After the patients were brought to the ward, the subsequent doses were 563.9 ± 262.8 mg in 24 hr and 868.3 ± 412.2 mg in 48 hr for tramadol, *vs* 28.0 ± 14.2 mg in 24 hr and 45.7 ± 18.4 mg in 48 hr for morphine. One patient in the tramadol group required rescue analgesic during the 48 hr. The mean frequency of PCA delivery was less in the tramadol group than in the morphine group at 24 hr (18.8 ± 8.7 *vs* 28.0 ± 14.2) ($P < .05$) and at 48 hr period (28.9 ± 13.7 *vs* 42.7 ± 18.4) ($P < .05$). The mean frequency of PCA demands was 34.0 ± 13.7 for tramadol, *vs* 32.1 ± 8.7 for morphine in 24 hr, and 43 ± 14.7 for tramadol, *vs* 48 ± 8.5 for morphine in 48 hr.

The overall satisfaction score in the recovery room, at 24 and 48 hr are summarized in Table II. "Very good" scores were more frequent in the morphine group than in tramadol group in the recovery room and at 24 hr interview. Otherwise there was no difference between the groups.

Nausea and vomiting was more frequent with tramadol than with morphine in the recovery room after the loading dose and in the first postoperative day, most of which, however, were transient in duration (Table III). Five, 12.5%, patients (four in the recovery room, one on ward) were treated with metoclopramide. Morphine showed more sedation than tramadol in both the recovery room and on the first postoperative day. None of the patients had a sedation score of 3 (unrousable sleep). None of the adverse effects warranted terminating PCA use. Vital signs were stable in both groups. No respiratory depression occurred in either group. Dizziness and dry mouth occurred more in the tramadol group but the difference was statistically insignificant.

TABLE I Demographic data and types of operation performed

	tramadol n=40	*morphine n=40*
Age	69 ± 13	71 ± 19
Sex (male:female)	18:22	15:25
Weight (kg)	56 ± 4	55 ± 6
Height (cm)	164 ± 7	163 ± 5
Total hip replacement	14	16
Total knee replacement	26	24

Data are mean ± standard deviation.

TABLE II Overall satisfaction rate

Time	*Drug*	*Satisfaction rate %* *very good*	*good*	*fair*	*poor*	*total*
recovery room	tramadol	23	43	30	5	40
after loading dose	morphine	43*	40	15	0	40
postoperative	tramadol	20	40	30	10	40
day 1	morphine	40*	48	13	0	40
postoperative	tramadol	83	13	5	0	40
day 2	morphine	80	15	5	0	40

*"very good" satisfaction rate is statistically more with morphine than tramadol in the recovery room and at 24 hr interviews (Chi-squared test).

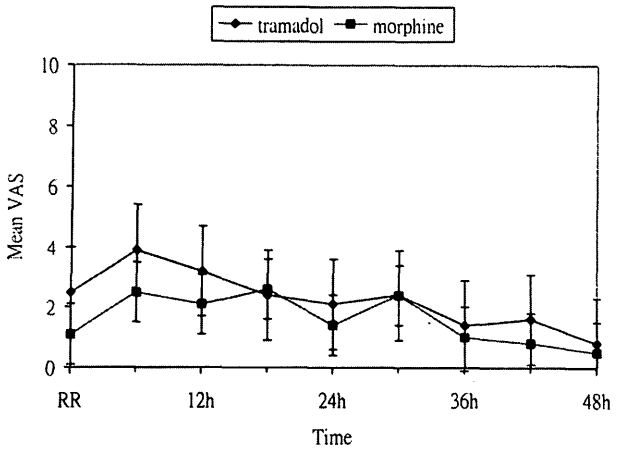

FIGURE The overall pain relief by VAS at each assessment. RR = recovery room (after the loading dose).

Discussion

This study demonstrated that, with the same PCA set up as morphine, tramadol at high dose provided effective analgesia similar to that of morphine but with a higher incidence of nausea and vomiting. Tramadol has a weak μ-agonist activity and a non-opioid mode of action presumably by blocking the re-uptake of serotonin and norepinephrine in the central nervous system.[3] Being a much weaker μ-agonist than morphine tramadol does not possess the euphoric and addictive liability that is associated with morphine.[8] In a study on the efficacy and safety of postoperative analgesia Houmes *et al.*[9] found less respiratory depression associated with tramadol than with morphine.

TABLE III Side effects observed during loading dose and PCA

Drug	*time*	*nausea*	*vomiting*	*dizziness*	*sleepiness*	*somnolence*	*pruritus*	*dry mouth*
Tramadol	RR	48*	28*	35	23	5	0	18
%	24hr	28*	15*	10	15	8	0	10
n=40	48hr	13	5	3	0	0	0	5
Morphine	RR	28	5	23	45*	10	3	8
%	24hr	12	3	3	35*	12	3	3
n=40	48hr	3	0	0	5	5	0	0

PCA = patient-controlled analgesia. RR = recovery room.
N = total number of patients in each group
Sedation scale 1 = drowsiness Sedation scale 2 = somnolence
Nausea, $*P < 0.05$ compared with morphine in recovery room and 1st postoperative day (Chi-squared test).
Sleepiness, $*P < 0.05$ compared with tramadol in recovery room and 1st postoperative day (Chi-squared test).

Tarradell *et al.*[10] in a single dose study comparing 100 mg tramadol with 100 mg meperidine for postoperative analgesia reported that meperidine induced sedation and respiratory depression while tramadol did not. This safety feature makes tramadol a very suitable analgesic to be used on the ward where intensive nursing monitoring is not the routine. In spite of the fact that tramadol has been available for clinical use for nearly two decades its use is marred somewhat by the controversies surrounding its analgesic efficacy.[11–14] Our study aimed to answer these two questions: (1) Can PCA tramadol provide satisfactory analgesia following major orthopedic surgery? (2) What is the true incidence of adverse effects, especially nausea/vomiting, when large doses of tramadol are given without anti-emetic prophylaxis?

To meet these objectives, we selected patients undergoing major orthopedic surgery, namely total hip and total knee arthroplasties for homogeneity, both of which are recognized to cause considerable postoperative pain. We choose PCA as a means of drug administration by which the patient would determine his/her own medication need while patient safety and avoidance of bias from the health care personnel were also achieved. We allowed the patients unrestricted loading doses of either tramadol or morphine in the recovery room under intensive surveillance until the patient obtained adequate pain relief with a VAS score of ≤ 4. No premedication, opioid or anti-emetics were allowed during surgery in order to remove the above important influencing factors on the incidence of nausea/vomiting associated with tramadol in the postoperative period. Analgesic was given immediately, as soon as the patient complained of pain in the recovery room. Since the patient is the ultimate judge of how good a drug is, global satisfaction assessments were made from the patient at each designated observation point. Lehmann *et al* in an open study using PCA tramadol in 40 patients with postoperative pain after gynecologic and orthopedic surgery, reported satisfactory analgesia in all but two patients with loading dose of 97.5 ± 42.3 mg (mean ± SD) and accumulated dose of 257 ± 102.8 mg in 24 hr.[15] In their multi-centre study, in which data from 523 patients were pooled from 26 hospitals, Vickers and Paravicini reported that with a loading dose of up to 250 mg tramadol *iv* in 90 min, 73% of the patients had "no" or "slight" pain, and the remaining 27% had to be excluded from the study.[16] Stamer and coworkers in a double-blind, randomized, and placebo-controlled study using self-administered PCA with a loading dose of tramadol up to 200 mg *iv* over 30 min found that only 67% had a VAS ≤ 2 in the tramadol group.[7] In a preliminary pilot study we found that, with a lockout interval of 10 min. and an equivalent dose of 11:1 mg (tramadol: morphine) as suggested by Vickers[4], tramadol was ineffective in achieving satisfactory analgesia in many patients. Hence, we adopted the ratio of 30:1 mg for tramadol:morphine in the present study and, by allowing an unrestricted loading dose of tramadol, we were able to achieve satisfactory analgesia (VAS < 4) in all the patients in the tramadol group. In our study, in order to achieve an effective initial analgesia the ratio of the loading dose for tramadol:morphine turned out to be 22:1 which was much higher than those reported by others.[7,16] This might explain the high incidence of non-responders reported by the other investigators[6,16] and a high incidence of nausea/vomiting observed in the tramadol group in our study.

We did not set a PCA limit on the dose of tramadol or morphine but relied on the lockout interval as well as the inherent safety of the PCA as a safeguard (e.g. the patient was instructed not to press the button if there

was no pain). As expected, our patients used a relatively higher dose of tramadol with a total of 868.3 mg *vs* morphine 45.7 mg over the 48 hr. This gives a potency ratio for tramadol: morphine at 19: 1 which is higher than the ratio of 11:1 reported by Vickers and Paravicini[17] and 11.8:1 reported by Stamer *et al.*[7] At this higher dose, however, all of the patients completed the study. More patients in the morphine group were found to have sleepiness than in the tramadol group ($P < 0.05$), but no respiratory depression was found in any of the patients in either group. More patients in the tramadol group had nausea/vomiting ($P < 0.05$).

Using such a high loading dose in 30 min resulted in an incidence of nausea (48%) and vomiting (28%) in the recovery room phase which was higher than that reported by Stamer *et al.*[7] and Vickers *et al.*[16] However, the incidence of nausea/vomiting in the above two studies was modified by the concurrent use of opioids or anti-emetics: anesthesia induction included 2.5 mg droperidol *iv* and 10 mg metoclopramide *iv* was given at 30 min before termination of the surgery in the study by Stamer *et al.*[7] The observed high incidence of nausea/vomiting in our study might be dose and rate related with the highest incidence occurring during the loading phase when a large amount of tramadol was given in a short period of time. It seems that a sudden increase of blood tramadol concentration would cause nausea/vomiting that was observed to be transient in nature in many of the patients. The incidence of nausea and vomiting declined to 12.5% and 5% respectively at 48 hr. To mitigate this adverse effect, a number of preventive measures could be adopted. De Witte *et al.* reported administering high doses of tramadol (3 $mg \cdot kg^{-1}$ *iv*) at the end of surgery without causing any adverse effect during the recovery period and shivering, nausea/vomiting were effectively prevented.[17] Ng *et al.* reported that a tramadol and droperidol mixture was superior to tramadol alone with less nausea/vomiting and without increased sedation.[18] Prophylactic administration of 10 mg metoclopramide *iv* before tramadol was also reported to be effective in reducing nausea/vomiting by Lehmann.[19]

In today's cost conscious health care environment, cost-benefit assessment of a drug needs to be addressed to allow clinicians to decide on the best analgesia at the lowest cost. In Taiwan, at equal potent dose, tramadol costs substantially more than morphine. In addition, the use of anti-emetics would entail added cost to the tramadol therapy. This high cost with the use of tramadol would need to be balanced against the potential benefit of less respiratory depression than morphine, which occurs quite infrequently, when delivered by PCA. Therefore, the clinical advantage of tramadol in this setting is more theoretical than practical.

In conclusion, the present study confirmed that PCA administration of tramadol could provide effective analgesia following major orthopedic surgery provided sufficiently high doses were given for loading and demand. However, the incidence of nausea and vomiting associated with the increased dose of tramadol is very high and results in decrease of patient satisfaction.

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