Intraoperative loading attenuates nausea and vomiting of tramadol patient-controlled analgesia

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Purpose: To evaluate the adverse effect profile of tramadol by patient-controlled analgesia (PCA) with administration of the loading dose either intraoperatively or postoperatively.

Methods: Sixty adult patients scheduled for elective abdominal surgery were enrolled into this prospective, randomized, double blind study. The patients were anesthetized in a similar manner. At the beginning of wound closure, the patients were randomly allocated to receive 5 $mg \cdot kg^{-1}$ tramadol (Group 1) or normal saline (Group 2). In the post-anesthesia care unit (PACU), when patients in either group complained of pain, 30 $mg \cdot ml^{-1}$ tramadol iv were given every three minutes until visual analogue scale (VAS) 3, followed by tramadol PCA with bolus dose of 30 mg and five minute lockout interval. Pain control and adverse effect assessments were done in the PACU and every six hours for 48 hr post drug by an independent observer.

Results: The loading dose was 290 ± 45 mg in Group 1 and 315 ± 148 mg in Group 2. In PACU, more nausea/vomiting both in terms of incidence (13/30, 43% *vs* 2/30, 6.6%, $P < 0.05$) and severity (nausea/vomiting score 2.5 ± 2.0 *vs* 0.2 ± 0.6, $P < 0.05$) was observed in patients with postoperative loading than in those with intraoperative loading of tramadol.

Conclusion: Administering the loading dose of tramadol during surgery decreases the nausea/vomiting associated with high dose of tramadol and improves the quality of tramadol PCA in the relief of postoperative pain.

Objectif : Évaluer le profil des effets indésirables du tramadol, utilisé pour l'analgésie contrôlée par le patient (ACP) après une dose de charge peropératoire ou postopératoire.

Méthode : Ont participé à l'étude prospective, randomisée et à double insu 60 patients adultes admis pour une intervention abdominale planifiée. L'anesthésie a été similaire pour tous. Au début de la fermeture de la plaie chirurgicale, les patients, répartis au hasard, ont reçu 5 $mg \cdot kg^{-1}$ de tramadol (Groupe 1) ou un soluté physiologique (Groupe 2). À la salle de réveil, on a administré sur demande 30 $mg \cdot ml^{-1}$ de tramadol *iv* à toutes les trois minutes jusqu'à ce que l'échelle visuelle analogique (EVA) indique ≥ 3. Puis, le tramadol ACP a été donné en bolus de 30 mg alternant avec une période réfractaire de cinq minutes. Le contrôle de la douleur et les effets négatifs ont été évalués par un observateur impartial à la salle de réveil et toutes les six heures pendant 48 h après l'administration du médicament.

Résultats : La dose de charge était de 290 ± 45 mg dans le Groupe 1 et de 315 ± 148 mg dans le Groupe 2. On a noté plus de nausées et de vomissements, en termes d'incidence (13/30, 43 % *vs* 2/30, 6,6 %; $P < 0,05$) et de sévérité (score de 2,5 ± 2,0 *vs* 0,2 ± 0,6; $P < 0,05$) dans le cas de la dose de charge postopératoire de tramadol que dans le cas de la dose peropératoire.

Conclusion : L'administration peropératoire d'une dose de charge de tramadol permet de réduire les nausées et vomissements associés à de fortes doses de tramadol et améliore la qualité analgésique postopératoire de ce médicament en ACP.

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TRAMADOL is a centrally acting analgesic with both opioid and non-opioid modes of action[1,2] and has been used for the relief of acute and chronic pain.[3,4] Its respiratory depressing effect is only that of a weak opioid at effective doses.[5] With a low abuse and addiction potential, tramadol is not a controlled substance in many countries. Therefore, it can be used for a much longer time than morphine. Unfortunately, the widespread use of tramadol for patient-controlled analgesia (PCA) is hindered by its major adverse effects of nausea and vomiting.[4]

In a previous study[6] we found that tramadol PCA provided effective analgesia following major orthopedic surgery but a high incidence of nausea (48%) and vomiting (28%) was observed following the initial dose of tramadol (5 $mg \cdot kg^{-1}$) in the post-anesthesia recovery unit (PACU). The present study was undertaken to determine whether tramadol PCA could provide effective analgesia after intra-abdominal surgery and whether administering the loading dose during surgery would reduce the postoperative adverse effect of nausea/vomiting associated with tramadol.

Methods

Following approval of the Hospital Research Committee and informed consent, 60 adult patients with ASA physical status of I and II undergoing elective abdominal surgery were enrolled into this prospective, randomized, double blind study. All patients were instructed on the use of the PCA device and pain assessment by Visual Analog Score (VAS, 0 = no pain, 10 = the most excruciating pain) during the preoperative interview and again in the PACU. Exclusion criteria included: (1) difficulty in communication or inability to use PCA, (2) allergy to the study drug, (3) history of severe hepatic, cardiopulmonary or renal disease (4) history of substance abuse (5) obesity with body weight > 120% of the ideal body weight.

Anesthesia was induced with 4 $mg \cdot kg^{-1}$ thiopental *iv* and 1 $mg \cdot kg^{-1}$ succinylcholine iv and maintained with isoflurane in N_2O 60% and oxygen 40%. Muscle relaxation was maintained with vecuronium. No local anesthetics, anti-emetics or non-steroidal anti-inflammatory drugs were administered 24 hr before or during surgery. During surgery at the beginning of wound closure (about one hour before the end of surgery), patients were divided into two equal groups by a double-blind and randomized design using a computerized randomization table. Patients in Group 1 received 5 $mg \cdot kg^{-1}$ tramadol *iv* (Tramtor®, Patron Chemical & Pharmaceutical Co. Taiwan) and those in Group 2 received an equal volume of normal saline as control. The drugs were prepared in identically appearing syringes and the anesthesiologists who administered it were blinded to its identity. The 5 $mg \cdot kg^{-1}$ tramadol dose was determined from a pilot study in PACU in which we gave differing loading doses of tramadol to achieve adequate analgesia. An initial dose for intra-abdominal surgery was about 5 $mg \cdot kg^{-1}$ to achieve the VAS 3. After drug administration, the inspiratory concentration of isoflurane was decreased according to the depth of anesthesia. At the last skin suture isoflurane was turned off and oxygen 100% was given The trachea was extubated after the neuromuscular blockade was reversed, eyes open, response to verbal commands, and the patient was awake.

After arrival in the PACU and as soon as the patient complained of pain, a baseline pain assessment was done with VAS, and intermittent doses of 30 $mg \cdot ml^{-1}$ tramadol *iv* were given every three minutes until VAS became 3. After the loading dose, the patient was kept in the PACU for observation for one hour. Then, the patients were connected to a PCA pump (Lifecare Infusor-4200, Abbott Laboratories, North Chicago, USA) containing 30 $mg \cdot ml^{-1}$ tramadol with a bolus dose setup 1 ml and a lockout interval of five minutes. The program was set to have no continuous background infusion or a four-hour dose limit. Rescue analgesia with 25-50 mg meperidine *iv* was allowed if the patient did not obtain adequate pain relief with six consecutive doses of tramadol.

Pain assessment was carried out with VAS evaluation every six hours for 48 hr post drug by an anesthesia resident who was blind to the identities of the drugs and not involved in the loading process. Data on dosing patterns, demand, delivery and total dose used were retrieved from the PCA computer memory. Blood pressure, heart rate, respiratory rate, side effects and rescue medications were recorded throughout the 48 hr observation period.

Nausea and vomiting were assessed on a 5-point scale: 0 = no nausea/vomiting; 1 = nausea for < 10 min and/or vomiting only once, requiring no treatment; 2 = nausea persisted > 10 min and/or vomiting twice, but not requiring treatment; 3 = nausea persisted > 10 min and/or vomiting > twice, requiring treatment; 4 = intractable nausea/vomiting not responding to treatment. Metoclopramide, 10 mg *iv*, was given as an anti-emetic when the vomiting score reached 3. Sedation was also assessed on a 5-point scale: 0 = awake and oriented; 1 = drowsy, or eyes closed but rousable to verbal command; 2 = sleep, rousable to mild physical stimulation; 3 = rousable to strong physical stimulation; 4 = unrousable sleep. Respiratory depression was defined as respiratory rate < 10 min^{-1} or a sedation score of 4, and

was treated with termination of PCA and administration of naloxone *iv* and/or assisted ventilation. Shivering was defined as visible gross tremor of the extremities, the trunk, or both and was treated with warming blanket and/or 25 mg meperidine *iv* as needed. Pruritus was treated on request with 5 mg diphenhydramine *iv*. A sedation scale of 4 was treated as respiratory depression. Urinary retention could not be evaluated due to the use of indwelling catheters in all the patients. Seizures, if occurred, were treated with 5 mg midazolam *iv* as needed.

Data for age, body weight, height, duration of surgery, PCA demand, and consumption, were analyzed with Student t test and reported as mean ± standard deviation. Nausea/vomiting scores and VAS scores were analyzed with Mann Whitney U-test. Chi-square test was used for sex, physical status, type of surgery, and the incidence of nausea and vomiting. Analysis of adverse effects was done by Fisher's exact test. A P-value < 0.05 was considered statistically significant.

TABLE I Demographic data and surgery performed

	group 1 *n=30*	*group 2* *n=30*
Age (yr)	67 ± 13	68 ± 14
Sex (F/M)	21/9	19/11
Weight (kg)	58 ± 9	62 ± 11
Height (cm)	162 ± 7	165 ± 8
ASA status (I/II)	14/16	13/17
Duration of operation (min)	226 ± 28	231 ± 42
Colonic resection	10	9
Abdominal hystoerectomy	20	21

Data are presented as mean ± standard deviation

Group 1 = intraoperative loading of tramadol

Group 2 = postoperative loading of tramadol

n = number of the patients.

There is no difference between the two groups (sex, physical status, and types of surgery are analyzed by Chi-square test, others by Student t test).

Results

There were no differences between the two groups in terms of the demographic data, or type and duration of surgery (Table I).

In Group 1 the average intra-operative loading dose of tramadol was 290 ± 45 mg. Only three patients (3/30) in Group 1 needed additional tramadol (range 30-90 mg) to achieve a VAS 3 (Table II).

All patients in Group 2 required tramadol with an average interval of 22 ± 15 min between the arrival in the PACU and the administration of tramadol. The VAS score before tramadol administration in Group 2 was 5.9 ± 3.1 which was higher than in patients in Group 1 at the corresponding time in PACU ($P < 0.05$) (Figure 1). In Group 2, the tramadol dose required to achieve a VAS 3 in 30 min was 315.0 ± 148.5 mg (Table II). Once adequate analgesia was attained, the VAS 3 could be maintained with PCA in all patients throughout the 48 hr study (Figure 1). In postoperative day 1, one patient in Group 1 and two in Group 2 requested rescue analgesia of 25 mg meperidine *iv* once. There were no differences between the two groups in terms of the numbers of PCA boluses delivered, demand, and tramadol consumption (Table II).

More severe nausea/vomiting was observed in PACU in patients in Group 2 with postoperative tramadol loading than in Group 1 with intraoperative loading both in terms of incidence (13/30, 43.3% *vs* 2/30, 6.6%, $P < 0.05$, Table III) and severity (nausea score 2.5 ± 2.0 *vs* 0.2 ± 0.6, $P < 0.05$, Figure 2). Four

TABLE II Tramadol consumption, number of PCA demands and deliveries

	group	*I-O*	*PACU*	*1st 24 hr*	*2nd 24 hr*	*total*
Tramadol	1	290 ± 45	6 ± 4	488 ± 116	242 ± 81	1026 ± 246
Consumption (mg)	2		315 ± 148	513 ± 201	250 ± 127	1078 ± 476
Number of	1	—	—	15.8 ± 4.7	7.6 ± 3.1	23.4 ± 7.8
PCA delivery	2	—	—	16.6 ± 8.2	8.7 ± 3.8	25.3 ± 12.0
Number of	1	—	—	17.2 ± 5.8	8.7 ± 2.9	25.9 ± 8.7
PCA demand	2	—	—	20.4 ± 8.7	11.5 ± 8.6	31.9 ± 17.3

PACU = postanesthesia care unit.

PCA = patient-controlled analgesia

Group 1 = intraoperative loading of tramadol at wound closure

Group 2 = postoperative loading of tramadol in PACU

I-O = intraoperative loading of tramadol at wound closure.

Values are mean ± SD.

There was no statistical significant difference between the two groups (by Student t test).

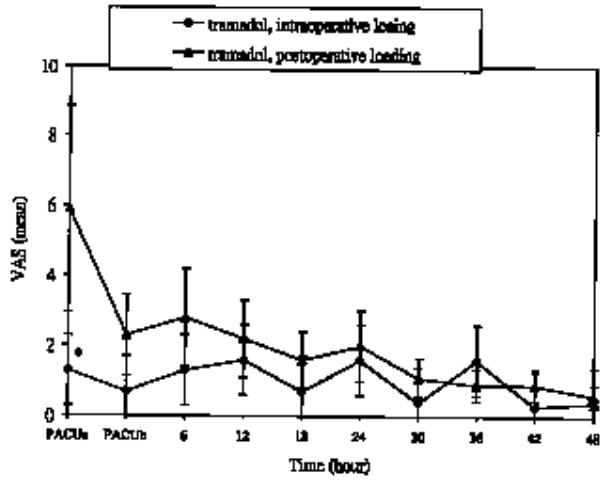

FIGURE 1 Overall pain relief by VAS at each assessment.
PACUa = In postanesthesia care unit, before loading dose of tramadol.
PACUb = In postanesthesia care unit, after loading dose of tramadol.
VAS = visual analogue scale.
*VAS ($P < 0.05$) between the groups before tramadol loading (PACUa) by Mann Whitney U test.

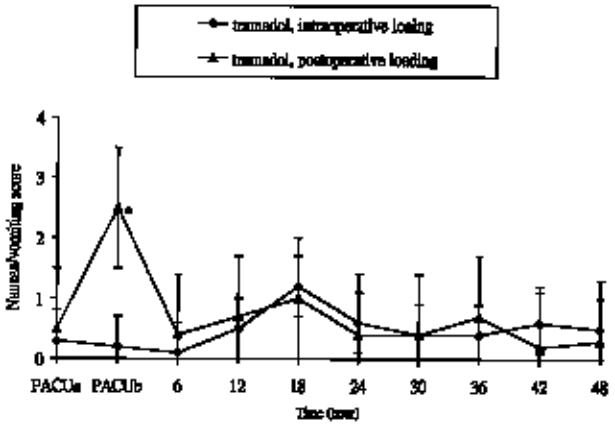

FIGURE 2 Nausea/vomiting scores (mean ± standard deviation).
PACUa = In postanesthesia care unit, before tramadol loading in group 2.
PACUb = In postanesthesia care unit, after tramadol loading in group 2.
*More nausea/vomiting with postoperative than intraoperative loading of tramadol ($P < 0.05$, by Mann Whitney U-test).

TABLE III Number of patients experiencing nausea and/or vomiting with PCA of tramadol.

Group	*PACU*	*1st 24 hr*	*2nd 24 hr*
Group 1 (n=30)	2 (6.6%)	7 (23.3%)	4 (13.3%)
Group 2 (n=30)	13 (43.3%)*	6 (20.0%)	3 (10%)

PCA = patient-controlled analgesia
PACU = postanesthesia care unit.
Group 1 = intraoperative loading of tramadol at wound closure
Group 2 = postoperative loading of tramadol in PACU
*More nausea/vomiting with postoperative than intraoperative loading of tramadol ($P < 0.05$, by Chi–square test).

patients in Group 2 required *iv* 10 mg metoclopramide treatment.

No other adverse effects were felt to be associated with intraoperative loading of tramadol. There was no statistical difference between the two groups in terms of other side effects such as shivering, sedation, dizziness, pruritus, dry mouth, etc., in PACU and in the 48-hr observation period. None of the patients had seizure, sedation scale of 4 (unrousable sleep) or respiratory depression. None of the adverse effects warranted terminating the PCA use and vital signs were stable in all patients.

Discussion

Our study demonstrates that PCA administration of tramadol can provide efficacious and safe analgesia following intra-abdominal surgery if sufficiently high doses are given for loading and by patient demand. The nausea and vomiting associated with the initial dose of tramadol (up to 5 $mg \cdot kg^{-1}$) in the PACU and in 48 hr observation was high. With regard to nausea/vomiting, the only differences between the two groups were seen in the PACU in which the initial dose of tramadol (up to 5 $mg \cdot kg^{-1}$) was given. However, administering the loading dose during surgery before the patient was waked from anesthesia nearly completely circumvented this adverse effect.

Although tramadol has been available for clinical use for nearly two decades, its use is hampered by the controversies surrounding its analgesic efficacy and the high incidence of nausea/vomiting.[4,7–9] Our study aimed to answer whether (1) PCA tramadol provides satisfactory analgesia following abdominal surgery and (2) if administering the loading dose during surgery can ameliorate the nausea/vomiting. To meet these objects we selected patients undergoing major intra-abdominal surgery that is known to be associated with considerable postoperative pain. We choose PCA for analgesic administration allowing the patient to deter-

mine the amount of medication needed and to avoid bias from the health care personnel. We allowed an unrestricted loading dose of tramadol until the patient obtained adequate pain relief with a VAS score of 3 in PACU. No premedication, or antiemetics were allowed before or during surgery in order to minimize the influencing factors on nausea/vomiting associated with tramadol in the postoperative period.

Our study showed that, by allowing an adequate loading dose of tramadol during surgery or in the PACU, we were able to achieve satisfactory analgesia in all patients. The nausea/vomiting that is associated with tramadol was decreased if the loading dose was administered during surgery. Our findings confirm the report by De Witte *et al.*[10] who studied intraoperative administration of at 3 $mg \cdot kg^{-1}$ tramadol for prevention of postoperative shivering, and made the casual remark that only one of the 20 patients receiving tramadol had postoperative nausea. It appears that the initial surge in blood concentrations of tramadol when a loading is administered over a relatively short time causes nausea/vomiting which may be mitigated because the patient is anesthetized and/or paralyzed. Once effective analgesia is established by the high loading dose, the relative "low" dose of tramadol administered by PCA would not result in a high incidence of nausea/vomiting. Being a weak opioid, tramadol at a dose of 5 $mg \cdot kg^{-1}$ did not cause clinically severe respiratory depression in this study. Different approaches to resolve the problem of tramadol-induced nausea/vomiting have been reported. Ng *et al.*[11] reported that a tramadol and droperidol mixture was superior to tramadol alone with less nausea/vomiting and without increased sedation. Prophylactic administration of 10 mg metoclopramide *iv* before tramadol was also reported by Lehmann[12] to reduce nausea/vomiting effectively. However, these studies were performed using small intermittent dose of tramadol and not with large loading dose and PCA infusion. Intraoperative loading would avoid the use of anti-emetic prophylaxis and improved the efficacy of tramadol PCA.

The toxicology of tramadol has to be addressed when a relatively large dose is to be employed. The reported LD_{50} on single *iv* injection of tramadol in rabbits, dogs, mice and rats ranges from 40 to 100 $mg \cdot kg^{-1}$.[13] In a prospective multi-centre evaluation of tramadol exposure, Spiller *et al.*[14] reported 87 cases of intoxication of tramadol in which 500 mg tramadol was the lowest dose associated with seizure, tachycardia, hypertension or agitation while 800 mg was the lowest dose associated with coma and respiratory depression. However, the toxic reaction was brief and self-limiting and severe cardiovascular toxicity, such as hypotension or arrhythmias, was not seen. General supportive therapy appeared to be sufficient in managing these overdose cases. With the loading dose of 5 $mg \cdot kg^{-1}$ not exceeding 500 mg, we did not observe any serious complications. However, for safety reasons, we would recommend a loading dose no higher than 5 $mg \cdot kg^{-1}$.

In conclusion, our study demonstrated that PCA administration of tramadol provides efficacious and safe analgesia following intra-abdominal surgery, as long as sufficiently high doses are given for loading and by patient demand. The high loading dose of tramadol at 5 $mg \cdot kg^{-1}$ after surgery is associated with more nausea/vomiting which can, however, be mitigated effectively by administering the loading dose during surgery.

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