Tramadol 2.5 mg·kg^{-1} appears to be the optimal intraoperative loading dose before patient-controlled analgesia

[Une dose de 2,5 mg·kg^{-1} de tramadol semble la dose d'attaque peropératoire optimale avant l'analgésie auto-contrôlée]

Wei-Wu Pang MD,* Hurng-Sheng Wu MD,† Chien-Chiung Tung MD‡

Purpose: We previously established that a 5 mg·kg^{-1} intraoperative dose can reduce the nausea/vomiting associated with tramadol patient-controlled analgesia (PCA). This study was conducted to identify the most appropriate initial dose to improve the quality of tramadol PCA.

Methods: During general anesthesia, 60 patients undergoing knee arthroplasty were randomly allocated to receive 1.25 mg·kg^{-1} (Group I), 2.5 mg·kg^{-1} (Group II), 3.75 mg·kg^{-1} (Group III), or 5 mg·kg^{-1} (Group IV) tramadol. The emergence condition was recorded. The titration of additional tramadol 20 mg + metoclopramide 1 mg doses by PCA every five minutes was performed in the postanesthesia care unit (PACU) until the visual analogue scale (VAS) score was ≤ 3. An investigator blinded to study group recorded the VAS and side effects every ten minutes.

Results: In the PACU, significantly more tramadol (8.4 ± 3.1 *vs* 4.3 ± 2.1, 2.5 ± 1.8, and 0.4 ± 0.3, $P < 0.05$), and a higher incidence (15/15 *vs* 5/15, 3/15, and 2/15, $P < 0.05$) of PCA use was observed in Group I compared to Groups II–IV. VAS was significantly higher in Group I than in Groups II–IV at zero and ten minutes ($P < 0.05$). Unexpected delayed emergence anesthesia (> 30 min) was observed in Group III ($n = 1$) and in Group IV ($n = 2$). Sedation was more important in Groups III and IV than in Groups I and II ($P < 0.05$).

Conclusion: When considering efficacy and side-effect profile, 2.5 mg·kg^{-1} of tramadol is the optimal intraoperative dose of this drug to provide effective postoperative analgesia with minimal sedation.

Objectif : *Il a été antérieurement établi qu'une dose peropératoire de 5 mg·kg^{-1} pouvait réduire les nausées et vomissements associés à l'analgésie auto-contrôlée (AAC). La présente étude voulait préciser la dose initiale la plus appropriée à une meilleure qualité de l'AAC au tramadol.*

Méthode : *Pendant l'anesthésie générale, 60 patients subissant une arthroplastie du genou ont été répartis au hasard et ont reçu 1,25 mg·kg^{-1} (Groupe I), 2,5 mg·kg^{-1} (Groupe II), 3,75 mg·kg^{-1} (Groupe III) ou 5 mg·kg^{-1} (Groupe IV) de tramadol. Les conditions du réveil ont été notées. Le titrage de doses supplémentaires de 20 mg de tramadol + 1 mg de métoclopramide administrées par AAC toutes les cinq minutes a été réalisé à la salle de réveil (SDR) jusqu'à l'obtention d'un score ≤ 3 à l'échelle visuelle analogique (EVA). Un expérimentateur impartial a enregistré les scores de l'EVA et les effets secondaires toutes les dix minutes.*

Résultats : *À la SDR, une quantité significativement plus importante de tramadol (8,4 ± 3,1 vs 4,3 ± 2,1, 2,5 ± 1,8 et 0,4 ± 0,3,$P < 0,05$) et une incidence plus élevée (15/15 vs 5/15, 3/15 et 2/15, $P < 0,05$) d'utilisation d'AAC ont été observées dans le Groupe I, comparé aux Groupes II– IV. Les scores à l'EVA ont été significativement plus élevés dans le Groupe I que dans les Groupes II–IV à zéro et dix minutes ($P < 0,05$). Un délai imprévu du retour à la conscience (> 30 min) a été observé chez les patients du Groupe III ($n = 1$) et du Groupe IV ($n = 2$). La sédation a été plus importante dans les Groupes III et IV que dans les Groupes I et II ($P < 0,05$).*

Conclusion : *Si on considère l'efficacité et les effets secondaires, on peut affirmer que 2,5 mg·kg^{-1} de tramadol constitue la dose peropératoire optimale permettant de fournir une analgésie postopératoire efficace et une sédation minimale.*

From the Department of Anesthesia,* Show-Chwan Memorial Hospital, Changhua; the Department of Surgery,† Show-Chwan Memorial Hospital, Changhua; National Defense Medical Center, and Tri-service General Hospital, Taipei; and the Department of Anesthesia,‡ Chen-Ching Hospital, Wu-Fong, Taichung, Taiwan, R.O.C.

Address correspondence to: Dr. Wei-Wu Pang, 7630 Pissarro Dr. Apt #108, Orlando, Florida 32819, USA. Phone: 407-351-8246; Fax: 407-351-8246; E-mail: sungfangrong@aol.com

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

Tramadol is a centrally acting analgesic with a mostly non-opioid mode of action.[1,2] It is effective for the relief of acute and chronic pain.[3,4] The adverse effect profile of tramadol, especially sedation and 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, tramadol PCA is hampered by its major side effects, nausea and vomiting.[4,7] We reported previously that by administering a 5 $mg \cdot kg^{-1}$ tramadol loading dose during surgery, the nausea/vomiting associated with tramadol PCA in the postanesthesia care unit (PACU) can be significantly reduced.[8] This is a follow-up study to determine the optimal intraoperative loading dose when tramadol PCA is used for postoperative pain control.

Methods

Following approval by the Hospital's Research Committee and after receiving patient informed consent, 60 adult patients ASA physical status I and II undergoing elective total knee replacement were enrolled into this prospective, randomized, double-blind study. All patients were instructed on the use of the PCA device and on pain assessment using the visual analogue score (VAS; 0 cm = no pain, 10 cm = the most excruciating pain) during the preoperative interview and again in the PACU. The 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; 6) history of previous postoperative nausea and vomiting (PONV).

Anesthesia was induced with *iv* fentanyl 100 μg, thiopental 4 $mg \cdot kg^{-1}$, and succinylcholine 1 $mg \cdot kg^{-1}$ and maintained with isoflurane in N_2O 60% and oxygen 40%. Vecuronium was used for muscle relaxation. No local anesthetics, anti-emetics or non-steroidal anti-inflammatory drugs (NSAIDs) were administered 24 hr before or during surgery. At the beginning of wound closure (about 40 min before the end of the procedure), patients were randomly divided into four equal groups using a computerized randomization table. Patients in Group I received tramadol (Tramtor®, Patron Chemical & Pharmaceutical Co., Taiwan) 1.25 $mg \cdot kg^{-1}$; Group II received 2.5 $mg \cdot kg^{-1}$; Group III received 3.75 $mg \cdot kg^{-1}$; and Group IV received 5 $mg \cdot kg^{-1}$. The drugs were prepared by a pharmacist in identically appearing syringes and the anesthesiologists administering the drug were blind to drug dose. After drug administration, the isoflurane inspiratory concentration was adjusted to maintain blood pressure and heart rate within appropriate limits. When the last skin suture was inserted, isoflurane was turned off, 100% oxygen given and the trachea extubated. Any unusual condition during emergence was recorded.

TABLE I Demographic data

	Group I (n = 15)	*Group II (n = 15)*	*Group III (n = 15)*	*Group IV (n = 15)*
Age (yr)	66.8 ± 11.7	67.4 ± 9.8	69.8 ± 7.9	67.9 ± 10.4
Sex (F/M)	9/6	10/5	8/7	11/4
Weight (kg)	59.1 ± 8.9	63.5 ± 7.4	61.1 ± 7.1	58.9 ± 9.2
Height (cm)	159 ± 6.1	163 ± 8.4	161 ± 9.4	158 ± 7.9
ASA status (I/II)	2/13	1/14	1/14	3/12

n = sample size; F/M = female/male; ASA = American Society of Anesthesiologists. Data are presented as mean ± standard deviation where appropriate. There were no significant differences between groups.

TABLE II Total volume of drugs delivered and incidence of PCA use in the postanesthesia care unit

	Group I (n = 15)	*Group II (n = 15)*	*Group III (n = 15)*	*Group IV (n = 15)*
PCA delivery (mL)	8.4 ± 3.1*	4.3 ± 2.1	2.5 ± 1.8	0.4 ± 0.3
Number of patients who used PCA	15/15†	5/15	3/15	2/15

PCA = patient-controlled analgesia; *n* = sample size. Each mL contains 20 mg tramadol and 1 mg metoclopramide. *$P < 0.05$ Group I *vs* Groups II, III, IV; †$P < 0.05$ Group I *vs* Groups II, III, IV.

TABLE III Incidence of side effects in operating room and postanesthesia care unit

	Group I (n = 15)	*Group II (n = 15)*	*Group III (n = 15)*	*Group IV (n = 15)*
Unexpected delayed emergence	0	0	1	2
Mild nausea	2	0	0	0
Vomiting	0	0	0	0
Sedation, grade 2/3	0/0	0/0	*4/0	*5/0
Dizziness	0	0	0	2
Pruritus	0	0	1	0
Dry mouth	0	0	1	2

n = sample size. *$P < 0.05$ Groups III and IV *vs* Groups I and II.

On arrival in the PACU, patients were connected to a PCA pump (Pain Management Provider, Abbott Laboratories, North Chicago, USA). A baseline pain assessment was done with VAS. When VAS was more than 4, PCA at the dose of 1 mL (containing 20 mg tramadol + 1 mg metoclopramide) every five minutes was administered until VAS ≤ 3. An investigator blinded to the study grouping carried out pain control (VAS) and side effect assessments that were recorded every ten minutes in the PACU for one hour. The addition of 1 mg metoclopramide to each 20 mg tramadol was based on a previous study in which we found that nausea and vomiting were significantly reduced with this combination throughout the 48-hr PCA period.[9] The investigator did not specifically ask about nausea; rather, those patients who reported nausea themselves or presented with the symptoms of nausea and/or vomiting were counted. Patients who had nausea for more than ten minutes and vomited twice or more, were categorized as having severe PONV and were treated with *iv* ondansetron 4 mg. The degree of sedation was scaled as: grade 0 = awake and alert; grade 1 = drowsy or eyes closed but can be aroused using only a verbal command; grade 3 = somnolence, arousable only by strong physical stimulation; grade 4 = unarousable sleep. Grade 3 and 4 sedation were treated with close observation, oxygenation and intubation if necessary. Data on PCA demand, delivery, and total consumption as well as blood pressure, heart rate, respiratory rate, and side effects were recorded. The patient was discharged to the ward at one hour if stable.

Analysis of variance (ANOVA) was used for demographic data analysis and PCA delivery. Results are reported as mean ± standard deviation. When differences between groups were statistically significant, the ANOVA was followed-up with the least significant difference test. The Chi-square test was used for categorical data. Chi-squared or Fisher's exact test were used for the incidence of side effects. The Kruskal-Wallis test and post-hoc Dunn test were used to analyze pain scores among the four groups. A P value of 0.05 was considered statistically significant.

Results

Demographics were similar among groups (Table I).

In the PACU, in order to achieve a VAS ≤ 3, more tramadol was required in Group I than in groups II, III, and IV (8.4 ± 3.1 *vs* 4.3 ± 2.1, 2.5 ± 1.8, and 0.4 ± 0.3, $P < 0.05$). The incidence of PCA use in the PACU was also more frequent in Group I than in Groups II, III, and IV (15/15 *vs* 5/15, 3/15, and 2/15, $P < 0.05$; Table II).

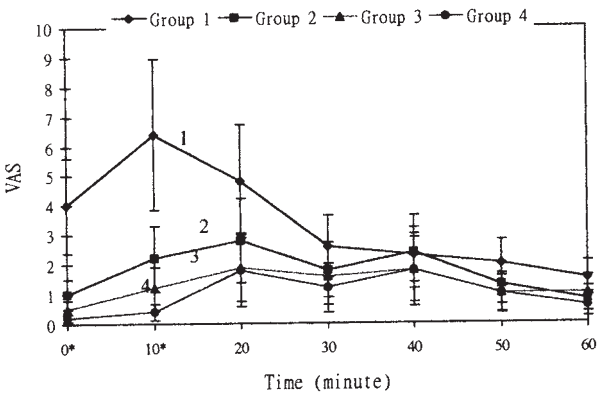

FIGURE Pain scores by visual analogue score (VAS) at each assessment time. Group I = tramadol 1.25 mg·kg^{-1}; Group II = tramadol 2.5 mg·kg^{-1}; Group III = tramadol 3.75 mg·kg^{-1}; Group IV = tramadol 5 mg·kg^{-1}; 0 = arrival in postanesthesia care unit. *$P <$ 0.05 Group I *vs* Groups II, III, and IV (at zero, ten minutes).

The pain score by VAS at each assessment is presented in the Figure. Group I had higher VAS scores than Groups II, III, and IV at zero and ten minutes ($P < 0.05$).

The incidence of side effects in the operating room and PACU is shown in Table III. Delayed emergence from general anesthesia was observed in one patient (lasted 35 min) in Group III and two patients (lasted 35 min and 60 min respectively) in Group IV. The incidence of grade 2 sedation was greater in Groups III and IV than in Groups I and II ($P < 0.05$). There was no statistical difference during the entire PACU observation period among the groups in terms of other side effects such as nausea, vomiting, dizziness, pruritus, dry mouth, etc. None of the patients had shivering, seizures, or respiratory depression. All patients had stable vital signs.

Discussion

This study suggests that a 2.5 mg·kg^{-1} intraoperative loading dose of tramadol is optimal. When tramadol was given at doses ≥ 3.75 mg·kg^{-1}, a greater incidence of sedation was observed in the PACU. In addition, three patients manifested unexpected delayed emergence from general anesthesia lasting longer than 30 min. Conversely, if a 1.25 mg·kg^{-1} intraoperative loading dose was given, inadequate pain control occurred necessitating the administration of additional analgesics in the PACU. Either under dosing such as in Group I or over dosing in Groups III and IV is undesirable since it does not offer satisfactory care in the PACU.

Various attempts have been made to improve postoperative pain relief by non-opioids to avoid adverse effects such as respiratory depression. Tramadol is an analgesic with a mostly non-opioid mode of action.[1] With *iv* administration it has an onset time of less than three minutes.[1,4] Its plasma half-life is six hours longer than that of morphine (two hours).[1,3,4] It would be an attractive alternative if its associated nausea and vomiting could be reduced. Since it is known that intraoperative loading reduces nausea/vomiting in the PACU,[5] the aim of this study was to determine the best possible loading dose.

We did not use doses greater than 5 $mg \cdot kg^{-1}$ in the design of this study, based on the report by Spiller *et al.*[10] In a prospective multi-centre evaluation of tramadol, they reported 87 cases of tramadol intoxication 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.[10] The toxic reaction was brief and self-limited, severe cardiovascular toxicity, such as hypotension or arrhythmias, was not seen and general supportive therapy appeared to be sufficient in managing these cases of overdose.[10] With a 5 $mg \cdot kg^{-1}$ loading dose, not exceeding 500 mg, we did not observe any serious adverse events. Conversely, intraoperative loading doses less than 1.25 $mg \cdot kg^{-1}$ appear of little benefit because of lack of analgesia in the PACU. We believe the two patients who had mild nausea in Group I may have been pain related, since nausea subsided as more tramadol was given.

Interestingly, when the initial dose was $\geq$ 3.75 $mg \cdot kg^{-1}$, three patients manifested unexpected delayed emergence from general anesthesia (greater than 30 min). It seemed that tramadol was synergistic with general anesthetic agents and prolonged emergence similar to other analgesics. However, Coetzee *et al.*[11] observed that tramadol causes a dose-dependent activation of the electroencephalogram, a finding in apparent conflict with our clinical observations.

In clinical practice, for those patients who receive general or regional anesthesia, we believe tramadol intraoperative loading and tramadol PCA are another option for postoperative pain control in addition to morphine, nerve blocks, or NSAIDs. However, 1 mg metoclopramide should be added to each 20 mg tramadol.[9]

Conclusion

An intraoperative dose of 2.5 $mg \cdot kg^{-1}$ tramadol was superior in analgesic efficacy to 1.25 $mg \cdot kg^{-1}$ and equivalent to 3.75 $mg \cdot kg^{-1}$ and 5 $mg \cdot kg^{-1}$ for postoperative pain relief after knee arthroplasty. Significant sedating side effects apear with doses greater than 2.5 $mg \cdot kg^{-1}$. Therefore, 2.5 $mg \cdot kg^{-1}$ appears to be the optimal intraoperative loading dose before tramadol PCA.

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