Patient-Controlled Analgesia with Tramadol Versus Tramadol Plus Lysine Acetyl Salicylate

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By using a patient-controlled analgesia (PCA) delivery system, we compared the clinical advantages and disadvantages of PCA with tramadol and PCA with a mixture of tramadol plus lysine acetyl salicylate (a soluble aspirin). Fifty adult patients who had undergone major orthopedic surgeries were enrolled into a prospective, randomized, and double-blinded study. The general anesthesia was performed in a standard manner. At the beginning of wound closure, an equal volume dose of either tramadol 2.5 mg/kg (Group 1) or tramadol 1.25 mg/kg + lysine acetyl salicylate 12.5 mg/kg mixture (Group 2) was administered slowly IV. These solutions were continued postoperatively for IV PCA. Pain control, patient satisfaction, vital signs, and adverse effects were assessed for 48 h. Visual Analog Scale ≤3 could be achieved with either group. Total tramadol consumption was significantly less in Group 2 than in Group 1 (614 ± 259 mg vs 923 ± 354 mg) ($P < 0.05$). Patients in Group 2 were more alert ($P < 0.05$). Blood loss from the surgical drain was similar, 865 ± 275 mL (Group 1) vs 702 ± 345 mL (Group 2). We conclude that aspirin can be used as an effective and safe adjuvant to tramadol for PCA after orthopedic surgery.

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Lysine acetyl salicylate (LAS), an injectable aspirin, could be used as an effective and safe adjuvant to morphine for patient-controlled analgesia (PCA). This combination reduces the morphine requirement, and hence, some of the morphine-related unfavorable effects (1). When used in PCA, tramadol alone can provide effective analgesia after major orthopedic surgery provided that a sufficiently large dose is given for both loading and patient demand. However, the incidence of nausea/vomiting is also more frequent, causing less patient satisfaction (2). The clinical benefit and disadvantage of PCA with a combination of tramadol and LAS is not known. Therefore, in a double-blinded and randomized manner, we compared PCA with tramadol versus tramadol plus LAS to determine any possible benefit from this combination.

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Methods

With the approval of the hospital's research committee and written, informed consent, 50 adult patients scheduled for elective total hip or total knee arthroplasty were enrolled in the study. All the patients were ASA physical status I and II. Exclusion criteria included: allergy to the study drugs, inability to use the PCA, difficulty in communication, refusal to participate, history of significant liver or kidney diseases, history of substance abuse, history of peptic ulcer disease, or bleeding disorders. All patients were instructed on the use of the PCA pump during a preoperative consultation session as well as the use of the Visual Analog Scale (VAS) with 0 being no pain and 10 being the most excruciating pain. All patients received a standardized general anesthesia with which the 4 mg/kg thiopental and 1 mg/kg succinylcholine were used for induction, and end-tidal isoflurane of 1%–2% in 60% N_2O and 40% O_2 was used for maintenance. Fentanyl 100 μg was allowed and was given at least 1 h before the end of surgery. All patients were catheterized for urinary output. No local anesthesia, other opioids, antiemetics, or nonsteroidal antiinflammatory drugs (NSAIDs) were used 24 h before or during surgery. An appropriate dose of vecuronium was used for muscle relaxation. At the beginning of

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wound closure, the patients were randomly allocated to receive the study drug IV over 30 min as an initial dose. Group 1 received tramadol 2.5 mg/kg. Group 2 received 1.25 mg/kg tramadol plus 12.5 mg/kg LAS. Syringes containing an equal volume of either tramadol 20 mg/mL or tramadol 10 mg plus LAS 100 mg/mL were prepared by a pharmacist and given to the investigator who was blinded to the identity of drug(s). Drug compatibility in mixing tramadol with LAS had been verified by the pharmacy. After the initial dose, the inspiratory concentration of isoflurane was decreased appropriate to the depth of anesthesia. At the last skin suture, isoflurane was turned off and pure oxygen was given. The neuromuscular blockade was reversed with 2.5 mg of neostigmine and 1 mg of atropine. The trachea was extubated after eye opening on command or after awakening.

In the postanesthesia care unit (PACU), the IV line was attached to the PCA pump (Lifecare Infusor-4200; Abbott Laboratories, North Chicago, IL) with the respective study drug(s) that was used for the initial dose. The PCA dose was set at 1 mL/bolus, with a lockout interval of 5 min. PCA was given either by the patients themselves or assisted by the PACU nurses if patients requested analgesics. Neither continuous background infusion nor 4-h maximal limit was set. Rescue analgesia with titration of meperidine 15–25 mg IV was allowed if the patient could not obtain adequate pain relief from the above PCA regimen.

VAS at rest was assessed every 6 h for 48 h by a blinded investigator. At the last interview of each 24 h period, the patient was also asked to inform the investigator about overall satisfaction with a Global Satisfaction Score, which was divided into "very good," "good," "fair," and "poor." Data of PCA demand, dose delivered, and total dose consumed were retrieved from the computer memory bank of the PCA device.

All adverse effects were recorded during the 48-h observation period. Persistent nausea (defined as feelings of nausea for more than 30 min) and vomiting more than twice was treated with IV metoclopramide 10 mg every 4 h on request. The degree of sedation was rated on a 4-point scale with 0 = awake, 1 = drowsy, 2 = somnolence but responded to verbal commands, or 3 = unarousable sleep. Intolerable dizziness and tinnitus was treated by temporary discontinuation of PCA. The respiratory depression was defined as respiratory rate below 10/min. Seizure, if it occurred, was treated with diazepam 5 mg as needed. Urinary retention could not be assessed because of the presence of the indwelling Foley catheter in all the patients. Pruritus was treated with IV diphenhydramine 10 mg every 6 h as needed. Total blood loss via the surgical drain was measured to assess the bleeding tendency of the two groups when the drains were removed.

Data for age, body weight, height, tramadol demand, and consumption were analyzed with a Student's *t*-test and reported as mean ± SD. VAS scores were analyzed with the Mann-Whitney *U*-test. The χ^2 test was used for sex, type of surgery, and satisfaction score. Fisher's exact test was used for the analysis of adverse effects. A P value <0.05 was considered statistically significant.

Results

The demographic data and the types of operations for the two groups were comparable and without significant difference (Table 1).

The intraoperative initial dose was 170.3 ± 16.8 mg of tramadol for Group 1 and 88.1 ± 11.5 mg of tramadol for Group 2, and most patients in either group reported VAS <3 in PACU. Six patients (6/25) in Group 1 and 7 patients (7/25) in Group 2 required additional analgesia with PCA (2.4 ± 1.6 times vs 0.2.6 ± 2.0 times, P = not significant) to achieve VAS ≤3. Other than additional analgesic, there were no adverse effects observed in the PACU.

Both groups achieved effective postoperative analgesia throughout the 48 h. The pain intensity by VAS at each assessment was not statistically different between the groups (Figure 1).

There were no statistically significant differences between the groups on three satisfaction score assessments (PACU, 24h, 48h) (Table 2). Six patients in Group 1 and 4 patients in Group 2 complained of persistent nausea or dizziness, and thus rated the satisfaction score as "poor" in 24 h. Two patients with nausea were treated with metoclopramide 10 mg IV, and 1 patient with dizziness was advised to withhold further PCA temporarily until dizziness subsided. None of them requested the termination of PCA.

The tramadol + LAS group showed a statistically higher frequency in demand than the tramadol group (total times 66 vs 46, $P < 0.05$) (Table 3). Tramadol consumption in Group 2, however, was significantly less than in the Group 1 (923 ± 354 mg vs 614 ± 259 mg) ($P < 0.05$).

Regarding adverse effects, the incidence of persistent nausea, vomiting more than two times, and a sedation score of 2, were more prevalent in Group 1. Tinnitus occurred more in Group 2 than in Group 1 (Table 4). However, the difference did not reach statistical significance. A sedation score of 1 was significantly more frequent in Group 1 ($P < 0.05$). Urinary retention was not assessed because of the presence of urinary catheters. No patient in either group had sedation scale 3 (unarousable sleep) or a respiratory rate of <10/min. The time interval during which the blood loss was assessed was 2–4 days. The total amount of blood loss from surgical drain was 865 ± 275 mL in

Table 1. Demographic Data and Types of Operations

	Group 1 (n = 25) tramadol	Group 2 (n = 25) tramadol + LAS
Age (yr)	74.4 ± 8.3	72.8 ± 9.6
Sex (male/female)	12/13	11/14
Weight (kg)	68.1 ± 6.7	70.5 ± 9.2
Height (cm)	164.1 ± 6.9	167.1 ± 8.7
Total hip replacement	8	7
Total knee replacement	17	18

Values are mean ± SD.
LAS = lysine acetyl salicylate.
Age, weight and height were analyzed by Student's t-test. Sex and types of operations were analyzed by χ^2 test. There was no difference between the two groups.

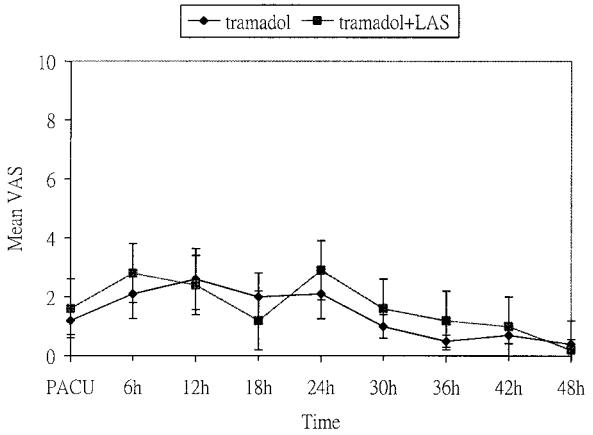

Figure 1. The overall pain relief by VAS at each assessment. PACU = postanesthesia care unit (after the intraoperative initial dose), LAS = lysine acetyl salicylate, VAS = Visual Analogue Scale. VAS (mean ± SD) showed no statistical difference between the two groups by Mann-Whitney U-test.

Group 1 and 702 ± 345 mL in Group 2 (P = not significant). None of the patients in either group complained of dyspepsia.

Discussion

This study demonstrated that parenteral aspirin could be used as an effective and safe adjuvant to tramadol PCA for postoperative analgesia in orthopedic surgery. This combination reduces the dose requirement of tramadol. These results indicate that the patients with tramadol and LAS were significantly more alert than with PCA tramadol alone. Although not reaching statistical significance, some other adverse effects associated with tramadol, such as nausea or vomiting, were reduced. It supports the concept that balanced analgesia is effective.

In alleviating postoperative pain, tramadol is an alternative drug to morphine for PCA treatment (2–4). Tramadol is a centrally acting analgesic with both opioid and nonopioid modes of actions (5,6). Its reputation for decreased opioid side effects, such as sedation, cardiorespiratory depression, and potential for abuse, fosters widespread use. Unfortunately, PCA with tramadol has been poorly used because of its principal side effect, namely, nausea (2,7).

Table 2. Global Satisfaction Score in PACU and Postoperative Interviews

Time/Drug(s)	Satisfaction Score No.				
	Very good	Good	Fair	Poor	Total
PACU					
Tramadol	9	11	5	0	25
Tramadol + LAS	7	15	3	0	25
24 h					
Tramadol	4	9	6	6	25
Tramadol + LAS	5	10	6	4	25
48 h					
Tramadol	12	9	3	1	25
Tramadol + LAS	16	5	3	1	25

PACU = postanesthesia care unit (after the intraoperative loading dose), No. = number of patients, LAS = lysine acetyl salicylate.
Global satisfaction rate on three interviews did not show a significant difference between the two groups by χ^2 test.

Lauretti et al. (8) reported that tramadol and piroxicam (a NSAID) is a useful multimodal balanced analgesia in both the intra- and postoperative periods. We found that when aspirin was added to tramadol PCA treatment, tramadol consumption could be decreased. This is similar to when NSAID was added to morphine PCA treatment (1,9,10)

The equal potency of tramadol and LAS was derived from the literature. Jones et al. (11) and Kweekel-De Vries et al. (12) reported an equal potency ratio 180:1 of morphine and aspirin. Vickers and Paravicini (3) and Stamer et al. (4) reported an equal potency ratio 11.1:1 and 11.8:1 of tramadol and morphine, respectively. We used an approximate extrapolated value of the two ratios, i.e., 10:1, for aspirin versus tramadol (3,4,11,12). By using this equal potency ratio, our study showed that the tramadol consumption in the tramadol/LAS group was decreased by approximately 33%, as shown in Table 3. This seems to indicate that the effect of a tramadol/LAS combination is additive and not synergistic. However, an isobolographic analysis is required to differentiate between synergy and additive effects. The selected intraoperative initial dose of tramadol at 2.5 mg/kg was determined from the results of a previous study, in which we found that the 2.5 mg/kg loading dose of tramadol provided adequate postoperative analgesia in the PACU with least delayed emergence (13). The initial dose of tramadol is associated with an increased incidence of nausea and vomiting if it is administered in the PACU (2). It is important to mention that we used the intraoperative initial dose. When using tramadol for PCA, an intraoperative initial dose decreases the nausea and vomiting associated with that dose (13).

Table 3. Frequency of PCA Demand (Attempt) and Doses of PCA Tramadol Delivery (Tramadol Consumption) of the Two Groups in PACU and Ward

Group	I-o initial	PACU	Day 1	Day 2	Total
Demand (numbers)					
Tramadol	—	2.4 ± 1.6	25.5 ± 16.3*	18.5 ± 3.2*	46.4 ± 21.1*
Tramadol + LAS	—	2.6 ± 2.0	34.4 ± 21.9	28.2 ± 14.6	65.2 ± 38.5
Tramadol consumed (mg of tramadol)					
Tramadol	170.3 ± 16.8	6.0 ± 4.0	410.3 ± 172.4	336.4 ± 160.9	923.0 ± 354.1
Tramadol + LAS	88.1 ± 11.5†	3.3 ± 2.5	240.3 ± 143.5†	282.6 ± 101.3†	614.3 ± 258.8†

Values are mean ± SD.
For dose value of LAS delivery, the equivalence is 1:10 mg (tramadol to LAS).
PCA = patient controlled analgesia, PACU = postanesthesia care unit, LAS = lysine acetyl salicylate, I-o = intraoperative.
* $P < 0.05$ compared with tramadol + LAS (*t*-test); † $P < 0.05$ compared with tramadol (*t*-test).

Table 4. The Incidence of Side Effects During the Use of PCA

Side effects	Tramadol (n = 25)	Tramadol + LAS (n = 25)	Significance
Persistent nausea	8	5	NS
Vomiting	3	2	NS
Drowsy	6	0	S
Somnolence	3	0	NS
Dizziness	4	5	NS
Tinnitus	0	2	NS
Dyspepsia	0	0	NS
Bleeding	0	0	NS

PCA = patient-controlled analgesia, LAS = lysine acetyl salicylate, NS = not statistically significant. (Fisher's exact test), S = statistically significant. Somnolence = asleep but responded to stimulation, bleeding = abnormal blood loss from drains.

The sedation was found to be significantly less with PCA tramadol/LAS than PCA tramadol alone. We believe that the presence of more alert patients in the tramadol + LAS group decreased acute cardiorespiratory depression and increased the PCA safety. This is especially important for a subgroup of patients, such as the elderly, severely chronically diseased patients, or those with alterations in consciousness, who are at risk for respiratory complications. Sedation is usually the first signal of central inhibition or respiratory depression. Two patients in the tramadol + LAS group had tinnitus. This could be aspirin related (14). The tinnitus subsided when the PCA was temporarily discontinued. The use of large doses of LAS in the tramadol/LAS group did not cause any significant postoperative bleeding problems, compared with that of the tramadol alone group. A significantly higher number of demands in the tramadol/LAS group suggested that pain control in this group may have been less adequate than in the tramadol alone group although the VAS ≤3 could be achieved in both groups.

In conclusion, our study showed that injectable aspirin could be used as an effective and safe adjuvant to tramadol for PCA in orthopedic patients.

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References

1. Pang WW, Mok MS, Ku MC, Huang MH. Patient-controlled analgesia with morphine plus lysine acetyl salicylate. Anesth Analg 1999;89:995–8.
2. Pang WW, Mok MS, Lin CH, et al. Comparison of patient-controlled analgesia (PCA) with tramadol versus morphine. Can J Anaesth 1999;46:1030–5.
3. Vickers MD, Paravicini D. Comparison of tramadol with morphine for post-operative pain following abdominal surgery. Eur J Anesthesiol 1995;12:265–71.
4. Stamer UM, Maier C, Grondt S, et al. Tramadol in the management of post-operative pain: a double blind, placebo- and active drug-controlled study. Eur J Anesthesiol 1997;14:646–54.
5. Raffa RB, Nayak RK, Liao S, Minn F. Mechanism(s) of action and pharmacokinetics of tramadol hydrochloride. Rev Contemp Pharmacother 1995;6:485–97.
6. Collart L, Luthy C, Dayer P. Partial inhibition of tramadol antinociceptive effect by naloxone in man. Br J Clin Pharmacol 1993;35:73.
7. Vickers MD. The efficacy of tramadol hydrochloride in the treatment of postoperative pain. Rev Contemp Pharmacother 1995;6:499–506.
8. Lauretti GR, Mattos AL, Lima IC. Tramadol and beta-cyclodextrin piroxicam: effective multimodal balanced analgesia for the intra- and post-operative period. Reg Anesth 1997;22:243–8.
9. Picard P, Bazin JE, Conio N, et al. Ketorolac potentiates morphine in postoperative patient-controlled analgesia. Pain 1997; 73:401–6.
10. Liaw WJ, Day YJ, Wang JJ, Ho ST. Intravenous tenoxicam reduces dose and side effects of PCA morphine in patients after thoracic endoscopic sympathectomy. Acta Anesthesiol Sin 1995;33:73–7.
11. Jones RM, Cashman JN, Foster JMG, et al. Comparison of infusions of morphine and lysine acetyl salicylate for the relief of pain following thoracic surgery. Br J Anaesth 1985;57:259–63.
12. Kweekel-De Vries WJ, Spierdijk J, et al. A new soluble acetyl salicylic acid derivative in the treatment of post-operative pain. Br J Anaesth 1974;46:133–5.
13. Pang WW, Hung CP, Chang DP, Huang MH. Intraoperative loading for tramadol PCA: a dose response study. Abstract accepted by the ASA annual meeting, San Francisco, CA, October 14–18, 2000.
14. Insel PA. Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LE, eds. The pharmacological basis of therapeutics. 9th ed. New York: McGraw-Hill, 1996;617–57.