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Original Research Articles

Effect on Pain Relief and Inflammatory Response Following Addition of Tenoxicam to Intravenous Patient-Controlled Morphine Analgesia: A Double-Blind, Randomized, Controlled Study in Patients Undergoing Spine Fusion Surgery

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Abstract

Objective. This study tested the hypothesis that adding tenoxicam (T) to intravenous patient-controlled analgesia (IV-PCA) with morphine (M) would improve postoperative pain relief and wound inflammatory responses compared with M alone after spine surgery.

Design. Randomized, prospective, double-blind, controlled study.

Subjects. Ninety-four patients eligible for elective spine surgery.

Setting. Teaching hospital.

Methods. Patients were randomized to one of three groups: the M group (PCA regimen with M), the TM group (PCA regimen with T and M), or the T+TM group (20 mg T administered 30 minutes before wound closure in addition to the TM regimen). The primary end point was the numeric rating scale score for pain intensity, and secondary end points pertaining to postoperative pain management included M consumption, PCA demand/delivery, use of rescue analgesics, adverse events, and levels of inflammatory mediators in wound drainages.

Results. PCA demand was reduced in both the TM and T+TM groups compared with the M group (both $P \leq 0.001$). The incidence of skin itching was significantly reduced in the T+TM group compared with the other groups (both $P \leq 0.05$). PGE_2 and interleukin-6 levels in wound drainages were reduced in the TM and T+TM groups compared with the M group (both $P \leq 0.001$).

Conclusions. The combination of T and M for IV-PCA was not more efficacious than IV-PCA with M alone in reducing postoperative pain after spine surgery but reduced PCA demand and suppressed

local inflammation at the surgical site. Administration of T before wound closure may ameliorate IV-PCA M-induced skin itching.

Key Words. Morphine; Tenoxicam; Patient-Controlled Analgesia; Postoperative Pain; Spine Surgery

Introduction

The phenomenon of postoperative pain as a consequence of many surgical procedures has been well-documented and applies to spine surgeries as well [1]. Pain, ranging from moderate to severe in intensity, often disrupts sleep, negatively impacts emotion, and impairs quality of life for patients during the postoperative recovery period [2]. A multimodal analgesia approach has become a standard of care in the current pain practice. For example, the addition of nonsteroidal anti-inflammatory drugs (NSAIDs) to opioids for analgesia can reduce opioid requirements by about 20–30% [3–7].

Tenoxicam (T), an NSAID extremely suitable for postoperative analgesia [8,9], has demonstrated both analgesic effects [10–15] and anti-inflammatory effects on the upregulated expression of prostaglandin E_2 (PGE_2), interleukin (IL)-6, and IL-8 in response to surgery [16–18]. This is particularly important because IL-6, IL-8, and PGE_2 have been implicated in the pathogenesis of pain [19–23].

Regarding NSAID use, single injections administered in a timely manner are generally recommended; however, intravenous patient-controlled analgesia (IV-PCA) provides better pain control than conservative treatment for postoperative acute pain following spine surgery. Therefore, the current randomized, double-blind, controlled study was designed to test the hypothesis that the combination of T with morphine (M) for IV-PCA (IV-PCA T/M) or combined treatment with a single IV injection of T (20 mg) 30 minutes before the end of surgery in addition to postoperative IV-PCA T/M was superior to IV-PCA with M alone for postoperative pain control. The primary end point was the numeric rating scale (NRS) score, and the secondary end points were adverse events, cytokine levels in exudates, dose of PCA M, and rescue analgesic requirements. Another objective of the current study was to identify correlations, if any, between wound drainage levels of the aforementioned inflammatory mediators and pain-related behaviors, such as high pain scores, increased analgesic consumption and dose delivery with PCA, higher frequency of PCA button pressing (PCA demand), and rescue M requirements in order to validate which mediators might be indicators of postoperative pain.

Methods

Participants

Following approval by the Institutional Review Board of Taipei Veterans General Hospital (TPVGH-IRB no. 96-07-02), we conducted this prospective, double-blind, randomized, controlled trial among patients who received elective spine surgery from September 2008 to November 2009. After obtaining written informed consent, patients between the ages of 18 and 80 with American Society of Anesthesiologist physical status I-III and scheduled for elective posterior spinal decompression, fusion, and instrumentation surgery were included in this study. Exclusion criteria included allergy to T, history of gastrointestinal (GI) bleeding, ulcer or perforation, renal or hepatic dysfunction, coagulopathy, asthma, persistent cardiac disease that may be aggravated by fluid retention or edema, inability to use the PCA device, and refusal to participate in the study. The operation of the IV-PCA (Abbott AIM Plus infusion pump; Abbott Laboratories, North Chicago, IL, USA) and instructions for using NRS (0 = no pain, 10 = worse pain imaginable) for the measurement of postoperative pain were explained beforehand to patients.

Treatment allocation was performed before site initiation. Permuted-block treatment allocation was used to randomly assign participants to each group. Patients meeting the inclusion criteria were randomly assigned in a 1:1:1 ratio to the M group with an M IV-PCA regimen, the TM group with IV-PCA T/M regimen, and the T+TM group with a single IV injection of T (20 mg) about 30 minutes before wound closure followed by the IV-PCA T/M regimen. In both the M and TM groups, a sham IV bolus of saline was administered 30 minutes before wound closure.

Anesthetic Protocol and Postoperative Analgesia

Analgesic drugs used before spine surgery were stopped for 5–7 days prior to the day of surgery, and a washout period was included in the study protocol. On the day of surgery, general anesthesia was induced with atropine 0.01 mg/kg, fentanyl 3 μg/kg, propofol 2 mg/kg, and rocuronium 1 mg/kg, and maintained with isoflurane in a 50% oxygen/air mixture to keep the end-tidal concentration of isoflurane at approximately 0.7–1.3 minimal alveolar concentration. At the conclusion of the surgical procedure, all patients received a closed-suction wound drainage tube. Muscle relaxation was reversed with atropine 0.01 mg/kg and neostigmine 0.05 mg/kg at the conclusion of surgery, and all patients were extubated in the operating room when awake and cooperative. After the surgery, patients were transferred to the post-anesthetic recovery room, and IV-PCA was immediately connected to initiate postoperative analgesia. The IV-PCA packages were prepared by a pharmacist and were marked only with a coded label to maintain the double-blind nature of the study. The packages were identical and were made up to contain M (100 mg; 1 mg/mL, pH 7.246) or a combination of M (100 mg; 1 mg/mL) and T (60 mg; 0.6 mg/mL; Tencam Lyo-Inj., 20 mg/vial; Standard Chem & Pharm Co., Ltd, Tainan County, Taiwan), each mixed with normal saline to produce a total volume of 100 mL solution (pH 7.353). PCA devices were programmed to deliver a loading dose of 0.05 mL/kg, continuous background infusion rate of 0.005 mL/kg/h, and bolus dose of 0.02 mL/kg

for each demand with a lockout interval of 10 minutes. For example, a 65-kg patient of IV-PCA T/M regimen would receive a 1.95 mg T and 3.25 mg M loading dose, a 0.195 mg/h T and 0.325 mg/h M background continuous infusion, and a 0.78 mg T and 1.3 mg M bolus dose. The lockout interval was set as 10 minutes.

Rescue analgesia was provided with IV M (2 mg) when resting NRS was ≥5. Staff regularly visited every patient for 3 days at postoperative hours 2, 8, 12, 24, 36, 48, 60, 72, and whenever needed. Additional visits were required for pain management on request or when adverse events or complications associated with IV-PCA occurred. NRS score, PCA demand/delivery, use of rescue analgesia, adverse events including nausea, vomiting, and wound drainage amounts were recorded at each time point. Respiratory depression was graded as: 1) mild, respiratory rate <10 breaths/minute, but no oxygen desaturation (oxygen saturation [SpO_2] > 90%); 2) moderate, respiratory rate ≤8 breaths/minute associated with oxygen desaturation (SpO_2 < 90%) that needed oxygen supplementation and naloxone reversal; and 3) severe, respiratory rate ≤8 breaths/minute with oxygen desaturation (SpO_2 < 90%) that needed aggressive oxygen support, naloxone reversal, and airway intervention. Moderate-to-severe respiratory depression was considered as a severe adverse event; the use of PCA was stopped immediately, and the patient was closely managed in the intensive care unit and withdrawn from the study.

Materials

Measures

The primary end point was the change in pain intensity based on patients' NRS scores as recorded during the 72-hour postoperative period. Secondary end points of postoperative pain management included cumulative M consumption, PCA demand/delivery, use of rescue analgesia, adverse events related to IV-PCA use (including skin itching, GI discomfort, nausea, vomiting, blood loss, and respiratory depression), and levels of inflammatory mediators in wound drainages within 72 hours after surgery. Safety end points consisted of moderate-to-severe respiratory depression and intolerable adverse events.

Assay of Inflammatory Mediators in Wound Drainages

Ten milliliters of wound drainage was collected from a hemovac drain at each visit with a serum separator tube, and the hemovac was subsequently cleared. The wound drainages were centrifuged at 2,000 × *g* for 10 minutes in a refrigerated centrifuge. Supernatants were then frozen and stored at –80°C until use. The frozen samples were thawed at 37°C before analysis. Concentrations of IL-6, IL-8, and PGE_2 in drainage supernatants were measured by sandwich enzyme-linked immunosorbent assay (ELISA) in 96-well microtitration plates following the manufacturer's protocols (R&D Systems, Minneapolis, MN, USA). The detection limits for the assays in pg/mL were: IL-6, 0.7; IL-8, 3.5; and PGE_2, 27.5. For all assays, the intraday and interday coefficients of variation were both less than 10%.

Statistical Analyses

Patients' age, body mass index and hemoglobin levels among groups M, TM, and T+TM were compared by one-way analysis of variance, and categorical variables were compared by chi-square tests. Continuous variables were represented as mean ± standard deviation, and number (N) and percentage (%) represented categorical data. Moreover, blood loss was compared by Kruskal–Wallis tests and represented as medians (interquartile range). Repeated measures, linear mixed models were used to determine the group effects in the changes of the NRS for pain measurement, M consumption (including total amount during the 72 postoperative hours and cumulative dose at each time interval), and inflammatory mediator analysis in the course of study. When a statistical difference between groups was apparent, multiple comparisons of means were performed using the Bonferroni procedure with type I error adjustment. In addition, IL-6, IL-8, and PGE_2 levels were logarithmically transformed due to their skewed distributions. The correlations between changes in cytokine concentration and pain intensity/pain NRS were determined using Pearson's correlation coefficients. All statistical assessments were two-sided and evaluated at the 0.05 level of significant difference. Statistical analyses were performed using SPSS 15.0 statistics software (SPSS, Inc., Chicago, IL, USA).

Results

Demographics

A participant flow diagram consistent with the Consolidated Standards of Reporting Trials (CONSORT) statement [24] is depicted in Figure 1. A total of 94 patients (34 in M group, 30 in TM group, and 30 in T+TM group) were randomly assigned to each of the three treatment groups, and five participants were excluded from final analysis. Two patients in the M group were excluded from analysis due to incomplete samples for ELISA analysis. One patient in the TM group was excluded from analysis due to a lack of a hemovac drain (necessary for ELISA analysis), and two patients in the T+TM group were excluded from analysis due to unanticipated analgesic (tramadol hydrochloride/acetaminophen) use during the course of the study. The final sample therefore consisted of 89 individuals: 32 (10 male/22 female) in M group, 29 (15 male/14 female) in TM group, and 28 (15 male/13 female) in T+TM group (Figure 1). The demographic and clinical characteristics were summarized in Table 1. There was no significant difference among these groups (all $P > 0.05$).

Postoperative Pain Management

Regarding the primary end point, NRS at ambulation was higher than the score at rest, although there were

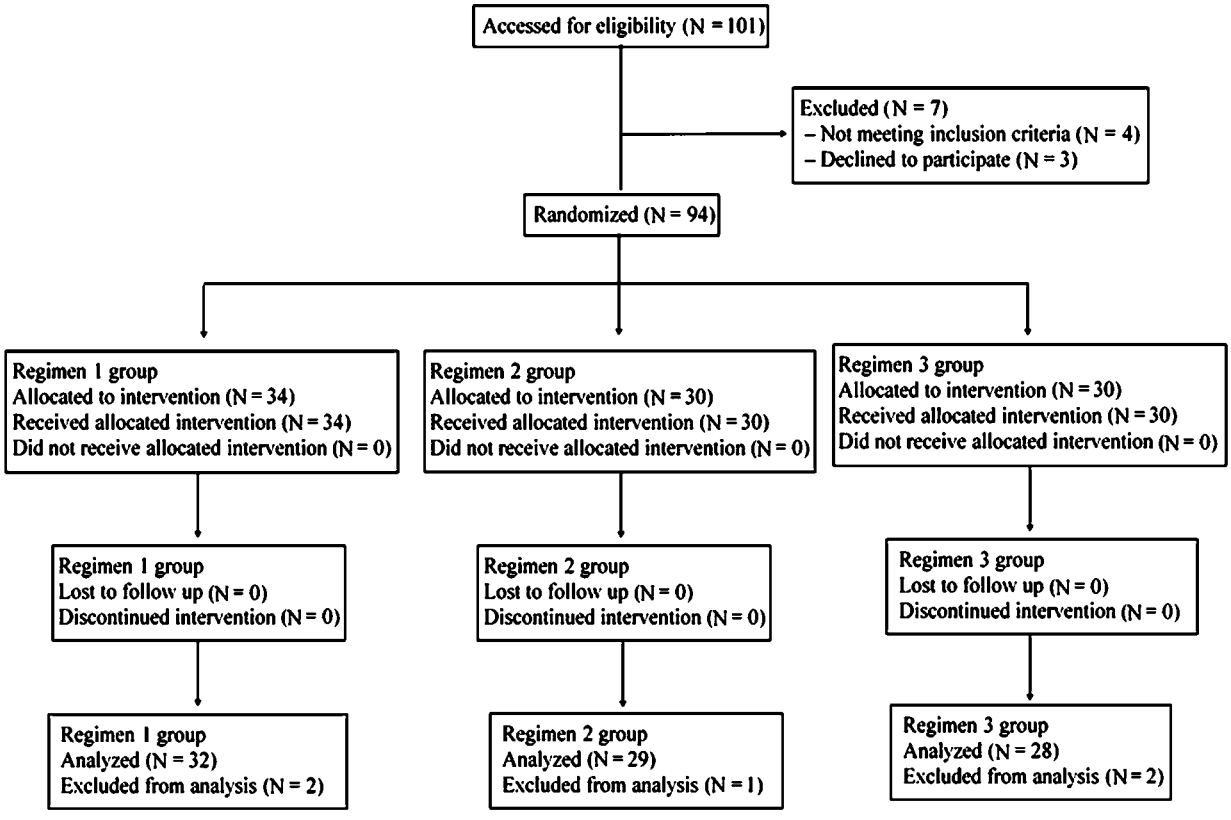

Figure 1 Participant flow diagram.

no significant differences in NRS among the three groups either at rest (Figure 2A, $P = 0.486$) or at ambulation (Figure 2B, $P = 0.614$). However, at 72 postoperative hours, the NRS score at ambulation in the T+TM group was significantly decreased in comparison with the M and TM groups, suggesting that administration of 20 mg IV T 30 minutes before wound closure subsequently followed by IV-PCA T/M was helpful in postoperative pain management.

The consumption measure was the M dosage used (mg), while the delivery measure was the number of patients using the push demand mode for PCA analgesia. Regarding the consumption of M, all patients needed less M during the first 12 hours post-surgery and then required more M in each subsequent time period. There was no overall group effect difference detected in cumulative M consumption (i.e., the sum of the PCA and rescue doses), although the TM group consumed more M during the three postoperative days and T+TM group members required less M during the 24- to 36- and 60- to 72-hour periods post-surgery (Figure 3A). Similar time-dependent trends in cumulative delivery (i.e., frequency of PCA medication delivered) during the first 72 hours after surgery were observed in M, TM, and T+TM groups, with no significant differences detected (Figure 3B, $P = 0.075$). However, T+TM group members needed less PCA delivery during the 24- to 36- and 60- to 72-hour periods than group M members (Figure 3B, 35.1% and 50.0% reductions, respectively, $P \leq 0.05$). In contrast, the cumulative demand (i.e., the frequency of pressing the PCA button for pain relief) was 42.4% lower in T+TM group than in M group at the 2-, 8-, 12-, 24-, 36-, 48-, 60-, and 72-hour measurement points, and the cumulative demand in the TM group was lower at the 2-, 8-, and 12-hour measurement points than in the M group (Figure 3C, both $P \leq 0.001$). However, the cumulative demand-time slope was similar between the M and T+TM groups but was higher during the 0–2, 2–8, 8–12, and 12- to 24-hour periods in the TM group than in the M group (Figure 3C). This parallel increase for cumulative data was related to both treatment effects and differences at the 2-hour measurement point. Although TM group members needed somewhat more cumulative rescue M doses, no statistical difference was detected, and a similar time-dependent trend in cumulative rescue M dose during the first 72 hours after surgery was observed among these groups (Figure 3D, $P = 0.109$). Furthermore, no significant differences were found in the ratios of demand and delivery among the three groups (data not shown). The average dosages of PCA T used in the TM and T+TM groups were 43.63 ± 3.89 mg and 38.10 ± 3.34 mg, respectively.

Table 1 Patient demographics

	Group M (N = 32)	Group TM (N = 29)	Group T+TM (N = 28)	*P* Value
Age (years)*	64.28 ± 9.13	62.83 ± 12.04	60.25 ± 12.27	0.376
BMI (kg/m^2)*	27.06 ± 3.79	25.62 ± 3.250	25.96 ± 3.84	0.274
Gender†				0.331
Male	10 (31.3%)	15 (51.7%)	15 (53.6%)	
Female	22 (68.8%)	14 (48.3%)	13 (46.4%)	
ASA†				0.445
I	13 (40.6%)	7 (24.1%)	8 (28.6%)	
II	14 (43.8%)	18 (62.1%)	13 (46.4%)	
III	5 (15.6%)	4 (13.7%)	7 (25.0%)	
Medical history†				
Hypertension	14 (43.8%)	13 (44.8%	7 (25.0%)	0.221
Diabetes mellitus	8 (25.0%)	4 (13.8%)	6 (21.4%)	0.543
Heart disease	7 (21.9%)	6 (20.7%)	4 (14.3%)	0.731
Neuropathic pain	24 (75.0%)	21 (72.4%)	20 (71.4%)	0.949
Analgesic taken†				0.050
NSAID	6 (18.8%)	2 (6.9%)	2 (7.1%)	
Opioid	3 (9.4%)	0 (0.0%)	0 (0.0%)	
NSAID + opioid	5 (15.6%)	4 (13.8%)	2 (7.1%)	
Preoperative Hgb (g/dL)*	13.30 ± 1.32	13.54 ± 1.26	13.59 ± 1.31	0.669
Segments of spine surgery‡				0.851
2 segments	11	10	11	
3 segments	13	14	12	
4 segments	7	3	4	
5 segments	1	2	0	
6 segments	0	0	1	
Operative time (min)*	205 ± 53	208 ± 58	212 ± 51	0.894
Blood loss (mL)‡	550 (350, 775)	500 (300, 800)	400 (300, 700)	0.359

Analgesic drugs used before spine surgery were stopped for 5–7 days prior to the day of surgery, and a washout period was included in the study protocol.
P values are based on: * ANOVA; † chi-square; and ‡ Kruskal–Wallis tests.
Data are represented as: * mean ± standard deviation; † number (%); and ‡ median (interquartile range).
ASA = American Society of Anesthesiologist physical status; BMI = body mass index; Hgb = hemoglobin; M = morphine; NSAID = nonsteroidal anti-inflammatory drug; T = Tenoxicam.

Adverse Events

The adverse events that occurred during the study are detailed in Table 2. The main adverse events were skin itching, GI discomfort (flatulence, belching, and/or constipation), nausea, vomiting, and transient and mild respiratory depression. Skin itching was the most frequently reported adverse event during 72 postoperative hours in

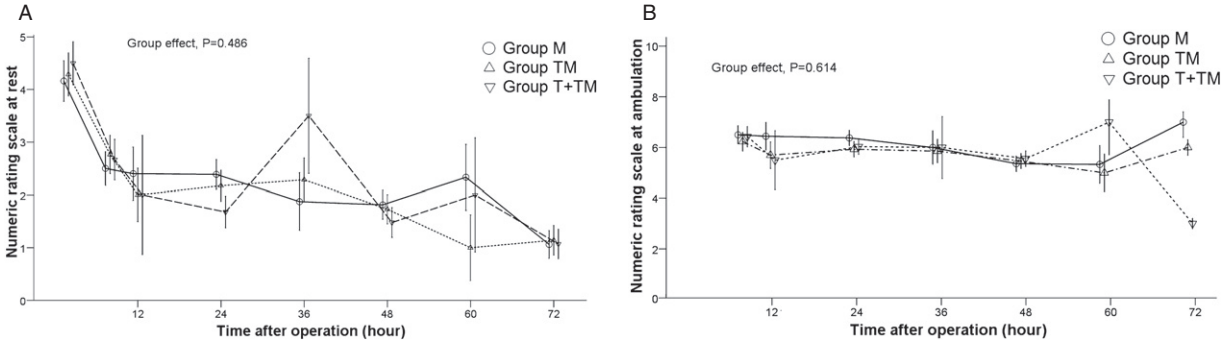

Figure 2 Pain numeric rating scale at rest (A) and ambulation (B) during 3 days postoperation. M = morphine; T = Tenoxicam.

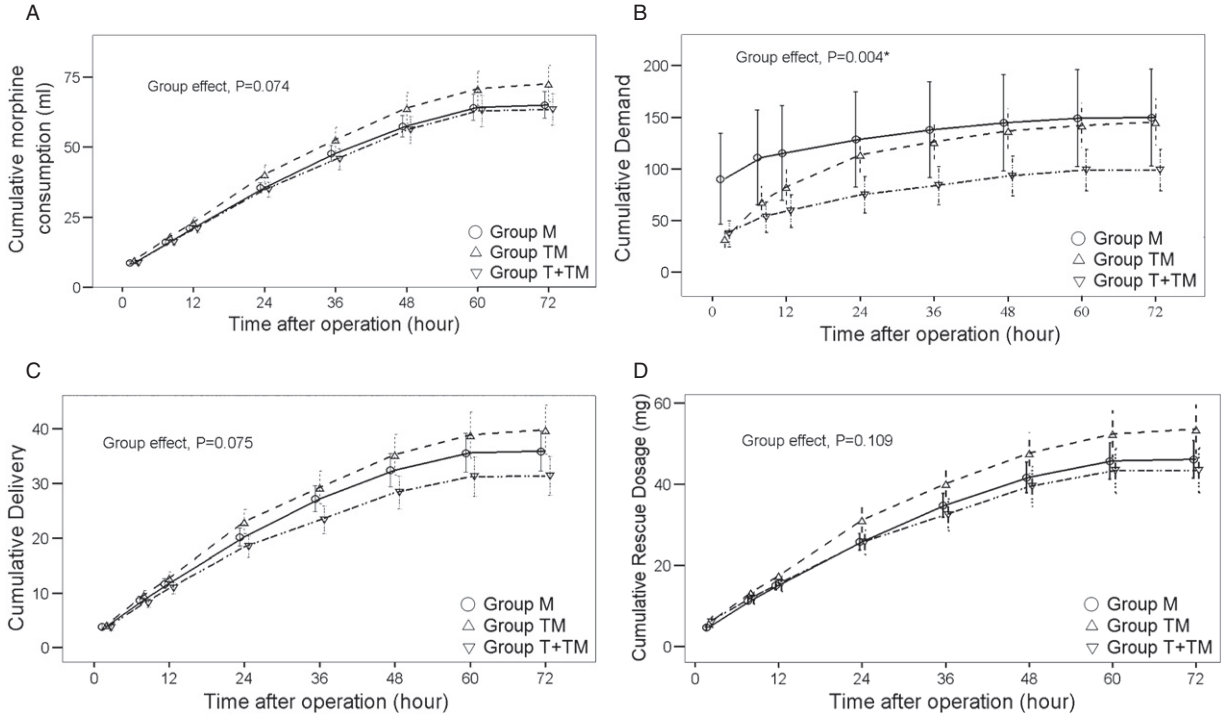

Figure 3 Average morphine cumulative consumption in each group during 72 postoperative hours (A), cumulative delivery (B), cumulative demand (C), and cumulative rescue morphine dose (D). The consumption measure was the dosage used (mg), the demand measure was the number of PCA button pushes, and the delivery measure was the number of successful attempts. M = morphine; T = Tenoxicam.

the study, but the incidence of skin itching was significantly lower in T+TM group than in M and TM groups (50% vs 78.1% and 50% vs 75.9%, respectively; $P < 0.05$). No intolerable and/or severe adverse events occurred. Although there were seven patients (7.9%) with mild respiratory depression, with respiratory rate at 8–10 times per minute, there was no desaturation in these patients, and no moderate or severe respiratory depression occurred.

Inflammatory Mediators in Exudates

Quantitative analyses of inflammatory mediators IL-6, IL-8, and PGE_2 in the wound drainages were performed during the first 3 days post-surgery (Table 3). IL-6 collected from wound drainages was increased at all measurement points from 2 to 72 hours after surgery, peaking at 24 hours (average increase = 21.2-fold) and diminishing gradually toward 72 hours (average increase = 8.2-fold)

Table 2 Adverse events

	Group M (N = 32)	Group TM (N = 29)	Group T+TM (N = 28)	*P* Value
Nausea, N (%)	14 (43.8)	19 (65.5)	11 (39.3)	0.102
Vomiting, N (%)	9 (28.1)	10 (34.5)	4 (14.3)	0.205
Gastrointestinal discomfort, N (%)	15 (46.9)	16 (55.2)	9 (32.1)	0.209
Itching skin, N (%)	25 (78.1)	22 (75.9)	14 (50.0)†‡	0.035*
Respiratory depression, N (%)	2 (6.3)	3 (10.3)	2 (7.1)	0.826

Number represents the total number of subjects with at least one event.
* Significant difference among the three groups using chi-square tests.
† Indicates a statistically significant difference between the indicated treatment group and group M.
‡ Indicates a statistically significant difference between the indicated treatment group and group TM.
M = morphine; T = Tenoxicam.

Table 3 Concentrations of inflammatory mediators IL-6, IL-8, and PGE_2 in exudates during 72 postoperative hours

	Time after Operation (hours)								*P* Value (Group Effect)
	2	8	12	24	36	48	60	72	
Log IL-6 (pg/mL)									<0.001*
Group M	1.52 ± 0.05	2.32 ± 0.03	2.70 ± 0.03	2.89 ± 0.02	2.88 ± 0.02	2.83 ± 0.03	2.70 ± 0.04	2.65 ± 0.10	
Group TM	1.40 ± 0.08	2.24 ± 0.04	2.58 ± 0.04	2.83 ± 0.03	2.73 ± 0.04	2.70 ± 0.05	2.55 ± 0.06	2.38 ± 0.08	
Group T+TM	1.40 ± 0.09	2.21 ± 0.05	2.67 ± 0.04	2.90 ± 0.05	2.91 ± 0.05	2.76 ± 0.07	2.64 ± 0.06	2.43 ± 0.05	
Log IL-8 (pg/mL)									0.071
Group M	1.68 ± 0.05	2.69 ± 0.04	2.98 ± 0.05	2.99 ± 0.06	2.93 ± 0.07	2.88 ± 0.06	2.96 ± 0.07	3.04 ± 0.12	
Group TM	1.57 ± 0.07	2.63 ± 0.05	2.92 ± 0.07	2.94 ± 0.09	2.85 ± 0.09	2.81 ± 0.08	2.87 ± 0.07	2.81 ± 0.11	
Group T+TM	1.56 ± 0.09	2.61 ± 0.07	2.97 ± 0.06	3.01 ± 0.08	2.95 ± 0.08	3.00 ± 0.09	3.06 ± 0.11	3.05 ± 0.08	
Log PGE_2 (pg/mL)									<0.001*
Group M	2.96 ± 0.04	3.00 ± 0.06	3.15 ± 0.07	3.40 ± 0.10	3.31 ± 0.10	3.10 ± 0.08	2.93 ± 0.09	2.82 ± 0.17	
Group TM	2.84 ± 0.06	2.92 ± 0.05	3.00 ± 0.07	3.00 ± 0.07	2.84 ± 0.07	2.67 ± 0.05	2.40 ± 0.07	2.11 ± 0.19	
Group T+TM	2.81 ± 0.04	2.84 ± 0.04	2.84 ± 0.05	2.78 ± 0.06	2.69 ± 0.05	2.63 ± 0.06	2.48 ± 0.10	2.51 ± 0.09	

* Significant group effect using linear mixed models.
IL = interleukin; M = morphine; PGE_2 = prostaglandin E_2; T = Tenoxicam.

compared with the 2-hour measurement (all $P \leq 0.001$). In addition, IL-6 levels were significantly higher in the M group when compared with those of the TM and T+TM groups, respectively (both $P < 0.001$). IL-8 collected from wound drainages was also increased at all measurement points from 2 to 72 hours after surgery, peaking at 24 hours (average increase = 23.8-fold) and lasting for 72 hours (average increase = 18.6-fold) compared with the 2-hour measurement. However, there were no significant differences in the concentrations of IL-8 among the three groups ($P = 0.071$). In M group patients, PGE_2 collected from wound drainages increased from 2 hours, peaking at 24 hours (5.4-fold increase) and declined to the 2-hour measurement toward 72 hours. There was a significant reduction in PGE_2 levels in wound drainages in both TM and T+TM groups compared with the M group (both $P \leq 0.001$). In the TM group, PGE_2 levels increased gradually, peaked at 24 hours (1.1-fold increase), and declined thereafter, falling below the 2-hour measurement from 48 to 72 hours. In contrast, PGE_2 levels remained steady in the T+TM group from 2 to 24 hours, and declined thereafter, reaching levels below the 2-hour measurement from 36 to 72 hours. PGE_2 levels at surgical sites were modulated by both the PCA T/M regimen and T administration 30 minutes before the end of surgery.

Correlation between Inflammatory Cytokines and M Consumption

Concentrations of PGE_2 were weakly positively correlated with M consumption (Figure 4A, $\gamma = 0.241$, $P = 0.023$), delivery (Figure 4B, $\gamma = 0.212$, $P = 0.046$), and rescue analgesic dose (Figure 4C, $\gamma = 0.283$, $P = 0.007$) during postoperative hours 8–12. Moreover, concentrations of IL-6 were significantly positively correlated with M consumption (Figure 4D, $\gamma = 0.713$, $P = 0.021$), demand (Figure 4E, $\gamma = 0.679$, $P = 0.031$), delivery (Figure 4F, $\gamma = 0.664$, $P = 0.036$), and rescue analgesic dose (Figure 4G, $\gamma = 0.668$, $P = 0.035$) during postoperative hours 60–72.

Discussion

Results from the current study demonstrated that there were no differences among these postoperative pain management groups with respect to the primary end point (NRS pain score) or the many secondary end points (cumulative M consumption, PCA delivery, ratio of demand and delivery, rescue M dose, incidence of GI discomfort, nausea, vomiting, and respiratory depression, and IL-8 levels in wound drainages). However, significant reductions in PCA demand were found in both the TM and T+TM groups, as well as significant reductions in IL-6 and PGE_2 in wound drainages. Additionally, IV administration of T (20 mg) 30 minutes before wound closure markedly reduced the incidence of skin itching during the three postoperative days in the T+TM group when compared with the M and TM groups. Based on these experimental results, the hypothesis that IV-PCA T/M or combined treatment with a single IV injection of T 30 minutes before the end of surgery and postoperative IV-PCA T/M

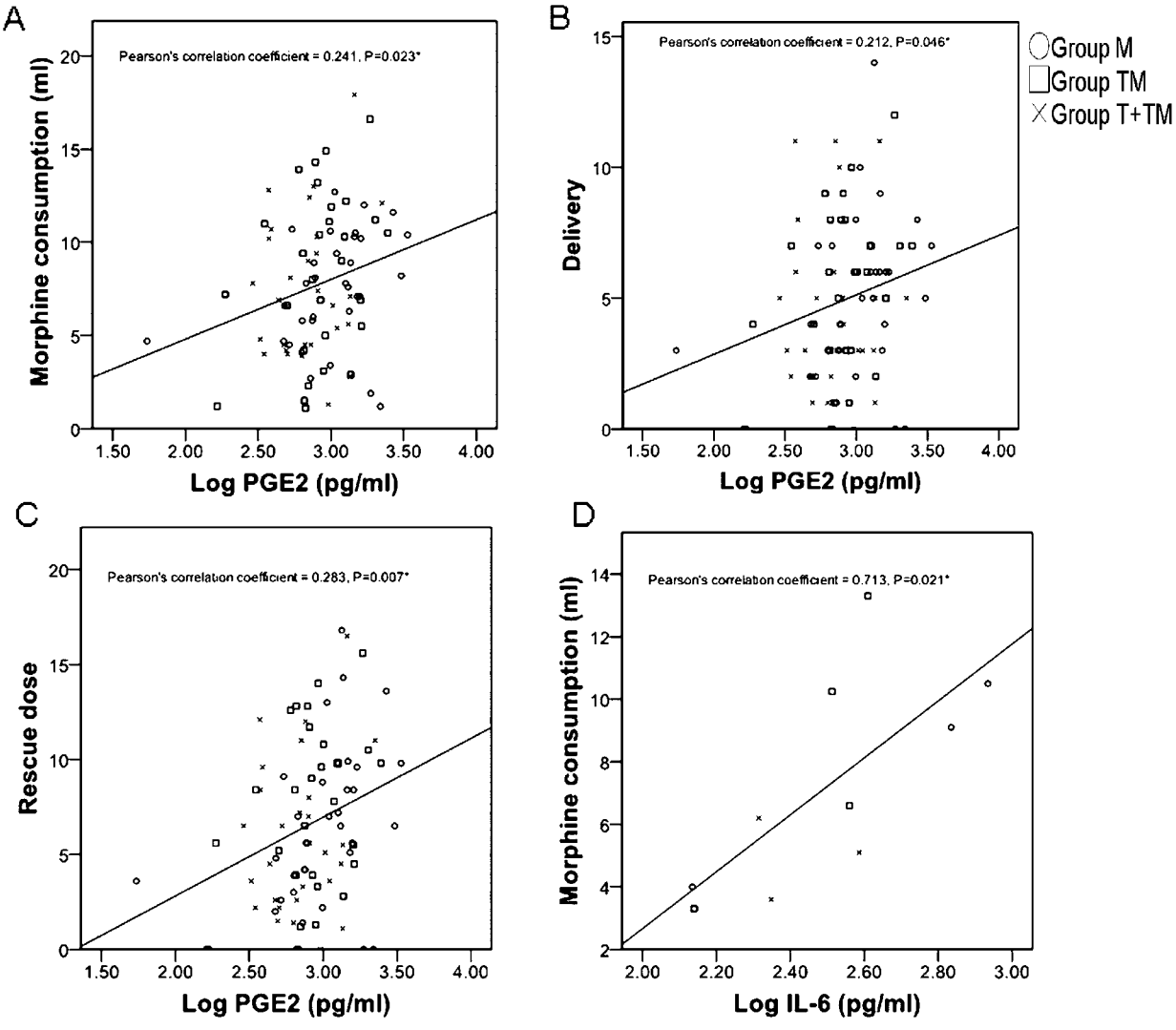

Figure 4 The correlations between changes in cytokine concentrations and pain intensity/pain numeric rating scale at each postoperative time interval. PGE_2 concentration correlated with M (A) consumption, (B) delivery, and (C) rescue dose. IL-6 concentration correlated with M (D) consumption, (E) demand, (F) delivery, and (G) rescue dose. IL = interleukin; M = morphine; PGE_2 = prostaglandin E_2; T = Tenoxicam.

was superior to IV-PCA M alone for reduced pain and analgesic requirements after spine surgery was rejected. However, these experimental treatment regimens improved the quality of postoperative pain management with regard to reduced PCA demand and incidence of skin itching, as well as suppressed PGE_2 and IL-6 production at the surgical site. No desaturation, or moderate or severe respiratory depression occurred in this study. Additionally, despite concerns regarding NSAID-related intraoperative bleeding, no abnormal intraoperative or postoperative bleeding occurred in our study at 1-year follow-up.

Multimodal analgesia has been shown to induce superior postoperative pain control as compared with M alone in many surgeries and several studies involving T for postoperative pain in different types of surgeries have reported results similar to those observed in the current study [12,13,15,25]. Based on the results of other studies, application of a single dose of T before or immediately after induction of anesthesia produced analgesic effects lasting for 24–48 hours postoperatively [6,13,26,27]. T, an NSAID in the oxicam group that inhibits both cyclooxygenase-1 and 2, takes about 30 minutes to onset, reaches a plasma peak concentration within 2 hours, and remains in the body with an average elimination half-life of 72 hours after drug administration [8,9]. T administered 30 minutes before wound closure in the T+TM group was intended to bring the within-group baseline analgesic effect as close to post-surgical recovery as possible. To our knowledge, other

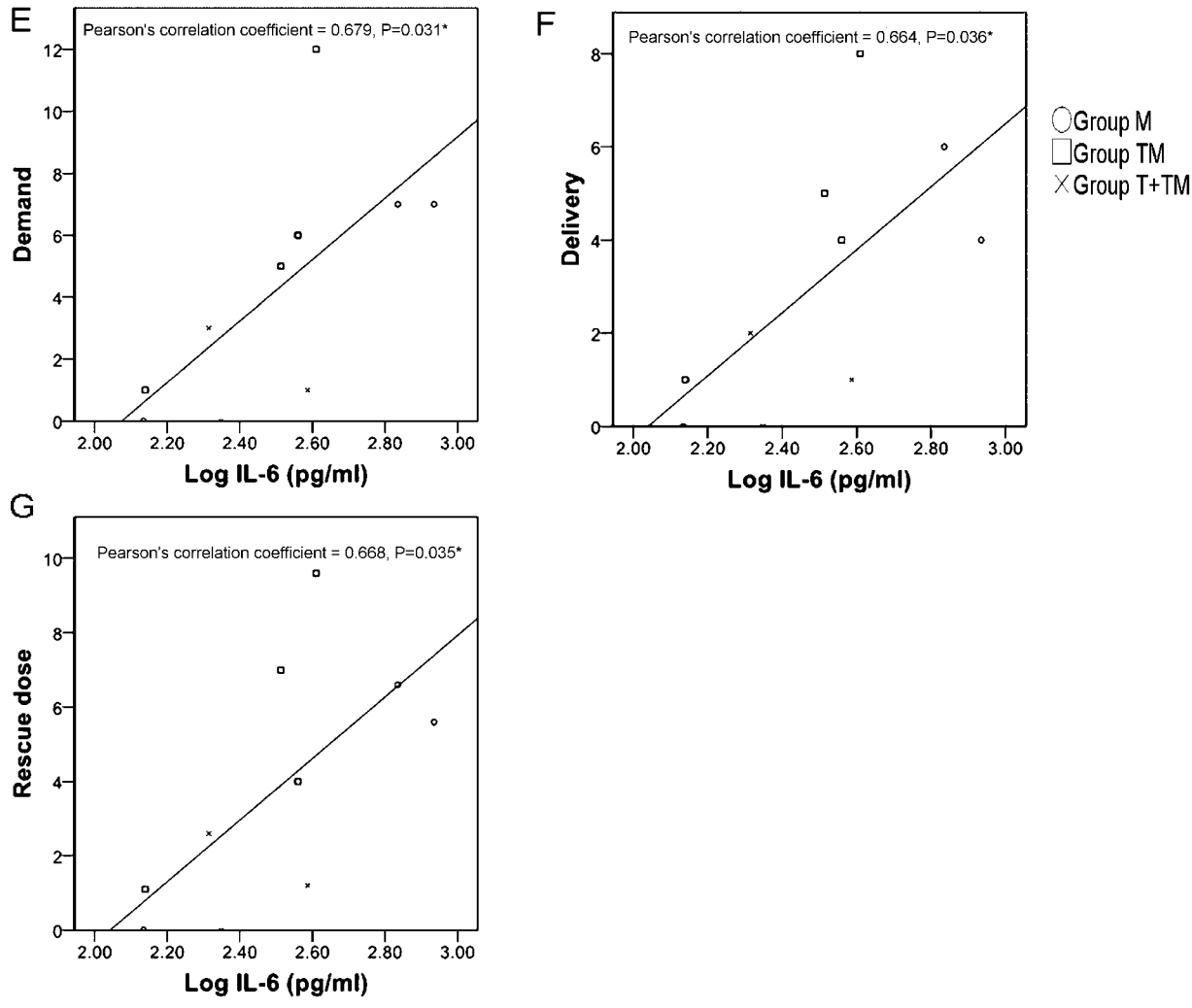

Figure 4 Continued.

reports of T administered by continuous infusion have not been described in the literature. Based on results of the current study, a relative paucity of clinical advantage in either pain relief (pain score) or M consumption in both the TM and T+TM groups over M group was observed. Pain scores (NRS) were low at rest and higher at ambulation, with no differences detected between the various treatment regimens. The IV-PCA T/M regimen did not improve postoperative pain relief during 72 hours after spine surgery when compared with the IV-PCA M regimen, and this finding may have been attributable to a variety of factors. For example, patients were strictly bedridden during the first 48 hours to 72 hours post-surgery, postoperative pain intensity after spine surgery may have been lower as compared with other major surgery or major orthopedic surgery, doses of PCA T may have been inadequate, and/or sufficient pain relief was achieved by the present IV-PCA M regimen. Further investigation may therefore be needed to elucidate the complexity of postoperative pain management after spine surgery. Current PCA guidelines recommend that only the patient should press the PCA button for pain relief (i.e., demand) and that greater frequency of PCA button pressing (demand) might be used as a negative quality indicator of postoperative PCA pain management. Although the cumulative demand in the TM group was lower at the 2-, 8-, and 12-hour measurement points than in the M group, the cumulative demand-time slope was higher at the 0- to 2-, 2- to 8- 8- to 12-, and 12- to 24-hour periods in the TM group than in the M group. Additionally, the effect of the IV-PCA T/M regimen on reducing the cumulative PCA demand after spine surgery resulted from both the PCA regimen and lower demand at postoperative hour 2. Therefore, the combination of T and M could only improve this quality variable of PCA therapy rather than reduce postoperative pain intensity. In addition, when T was administered 30 minutes before the conclusion of the operation and followed by a postoperative IV-PCA T/M regimen, not only a profound PCA demand-reducing effect was detected, but also a reduced incidence of PCA M-related skin itching was found. These results suggest

that T administered 30 minutes before wound closure could further improve the quality of postoperative PCA therapy with lesser side effects than IV-PCA M. Therefore, results of the current study indicated that the beneficial effects of administering T 30 minutes before the conclusion of the operation followed by a postoperative IV-PCA T/M regimen in patients after spine surgery were reduced PCA demand and a reduced incidence of PCA M-related skin itching.

Tissue injury following trauma or surgery can produce inflammatory responses and pain. Furthermore, the intensity of nociceptive pain has been suggested to be proportional to the magnitude of tissue injury and production of inflammatory mediators [28]. PGE_2, an inflammatory mediator, has been shown to directly excite nociceptors to induce pain [29] and/or indirectly stimulate the release of pain-related neuropeptides including substance P and calcitonin gene-related peptide from nociceptors [30]. IL-6 and IL-8, inflammatory cytokines, are key mediators in the generation of pain and development of tissue hyperalgesia [31–33]. IL-6, moreover, plays an important role in bone inflammation/pain by increasing osteoclastic activity [20,34,35] and involves generation of neuropathic pain after peripheral nerve injury in an animal model [36,37]. In the current study, increases of IL-6 and IL-8 were observed following surgery and peaked during postoperative hours 12–24 in wound drainage, as reported in other studies [16,18,38], although additional studies have demonstrated earlier postoperative peaks of IL-6 and IL-8 at 4–7 hours [17,39]. This might be due to differences in patient populations and disease entities, surgical procedures, anesthetic methods, methods of drainage fluid collection, etc. Intervertebral disc-macrophage interaction in situ, as revealed by extensive macrophage infiltration into the intervertebral disc autograft with marked upregulation of IL-6, IL-8, and PGE_2 messenger RNAs in vivo; and increased production of IL-6, IL-8, and PGE_2 in the intervertebral disc and macrophage coculture in vitro, has been shown to play a major role in sciatica in both autologous intervertebral disc autograft and spinal nerve ligation models in rats [22]. In addition, total hip replacement surgery has been associated with postoperative upregulation of PGE_2, IL-6, and IL-8 in both cerebrospinal fluid and wound drainage in humans; however, plasma levels of these inflammatory mediators were not found to be correlated with levels in cerebrospinal fluid in these patients [16]. Additionally, levels of IL-6 and IL-8 in wounds have been found to be higher than those in plasma in patients after mammoplasty and total hip replacement surgery [16,17]. Therefore, there were two reasons to examine levels of inflammatory mediators in wound drainage as opposed to plasma in the current study: 1) to determine the effect of different regimens for postoperative pain management on downregulation of local inflammatory responses at surgical sites; and 2) to determine correlations between levels of inflammatory mediators and pain-related behaviors.

As previously mentioned, T is an NSAID and as such is expected to have anti-inflammatory effects [40]. In fact, T has already demonstrated anti-inflammatory effects on nociceptive mediators that are implicated in pain processes [19], such as PGE_2, IL-6, and IL-8 [16–18]. Additionally, NSAIDs other than T, such as flurbiprofen and parecoxib, have also been reported to attenuate IL-6 in patients undergoing thoracotomy and surgery for colorectal cancer, respectively [41,42]. Preventing the increase of these mediators is important, as it can contribute greatly to analgesia via the clinical benefit of decreasing inflammation. In addition, PGE_2 production can be strongly inhibited by treatment with T in macrophages in vitro [43]. In contrast, there are concerns about potential hazards associated with NSAIDs, such as diminished bone formation, healing, and remodeling. For these reasons, it has been suggested that NSAIDs should be avoided in spine fusion surgery [44]. Although IV T was limited to short-term use during only the first three postoperative days, unfavorable effects on bone healing should be noted. In the current study, both PGE_2 and IL-6, but not IL-8, in the wound drainage from patients after spine surgery were significantly lower in the TM and T+TM groups than in the M group during 72 postoperative hours. These findings are suggestive of an anti-inflammatory response on surgical site PGE_2 and IL-6 production through the use of combined low-dose T and M infusion either with or without an initial loading dose of T (20 mg). Additionally, the increase in wound drainage IL-6 levels was positively correlated with M consumption, PCA demand, PCA medication delivery, and rescue M dose at the 60- to 72-hour measurement period after spine surgery that may explain why T+TM group patients needed less M and PCA demand/delivery at this time. In contrast, correlations between wound drainage PGE_2 levels and M consumption, PCA delivery, and rescue M dose during postoperative hours 8–12 were very weak, and their statistical significance was likely facilitated by the sample size. Therefore, the result of a robust correlation analysis remains to be elucidated. Results from the current study further demonstrated that PGE_2 levels in wound drainages may represent a weak predictor of pain-related behavior during postoperative hours 8–12 and that IL-6 in wound drainages may be a positive biochemical indicator of postoperative pain-related behavior but not pain intensity during postoperative hours 60–72. Collectively, these data suggest that T administered 30 minutes before the conclusion of the operation followed by a postoperative IV-PCA T/M regimen in patients after spine surgery not only reduced PCA demand and the incidence of PCA M-related skin itching but also suppressed PGE_2- and IL-6-related inflammatory responses at the surgical site.

Study limitations included the collection of wound exudates over a period of time, at variable rates, and from variable sources, and the inherent difficulty in correlating an inflammatory mediator to a particular time point. Although the use of a background infusion for IV-PCA is considered to be nonstandard and would therefore seem to have reduced clinical applicability, previous studies suggested the effective use of T as an analgesic drug by IV injection at individual doses on schedule, such as 20-mg

injections for 3 days (total dose of 60 mg). The dosage of IV-PCA T used in this study was based on the recommended dosage of IV T for acute postoperative pain management (60 mg/3 days); therefore, a drug combination of T 60 mg with M 100 mg for IV-PCA medication was designed. This IV-PCA T/M regimen had been safely used in a preliminary test, and the PCA protocol in this study adopted that of IV-PCA M empirically used for postoperative acute pain management in patients after spine surgery in our institution. It is possible that the dosage of IV-PCA T was too low to provide satisfactory pain relief in these patients. Further investigations to elucidate the optimal dose of T for IV-PCA would provide guidance regarding whether NSAIDs could be used for continuous infusion with IV-PCA or should be used only for intermittent IV injection for postoperative pain management.

In summation, the results of the current study suggested that: 1) the postoperative IV-PCA T/M regimen did not improve postoperative pain control but reduced the PCA demand compared with IV-PCA M alone; 2) an IV bolus of T before wound closure followed by the IV-PCA T/M regimen was more effective than the IV-PCA T/M regimen alone for reducing the incidence of skin itching; 3) the postoperative PCA T/M regimen either with or without a dose of T before the end of surgery could significantly suppress PGE_2 and IL-6 production at the surgical site; and 4) both PGE_2 and IL-6 could be humoral indices of postoperative pain. The combination of T with M for IV-PCA was not better than IV-PCA M alone for reducing postoperative pain intensity in patients after spine surgery. The addition of 20 mg of T before the end of the operation reduced the incidence of IV-PCA M-induced skin itching.

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