Intraarticular Tramadol-Bupivacaine Combination Prolongs the Duration of Postoperative Analgesia After Outpatient Arthroscopic Knee Surgery

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BACKGROUND: Intraarticular (IA) local anesthetics are often used for the management and prevention of pain after arthroscopic knee surgery. Recently, IA tramadol was also used for the management of these patients. However, the IA combination of local anesthetic and tramadol has not been evaluated in arthroscopic outpatients. Our primary aim in this study was to evaluate the analgesic effect of an IA combination of bupivacaine and tramadol when compared with each drug alone using visual analog scale (VAS) pain scores in patients undergoing day-care arthroscopic knee surgery. Additionally, we assessed analgesic demand.

METHODS: Ninety ASA I/II patients undergoing arthroscopic partial meniscectomy, performed by a single surgeon under general anesthesia, were assigned in a randomized, double-blind manner into three groups: group B ($n = 30$) received 0.25% bupivacaine, group T ($n = 30$) received 100 mg tramadol, and group BT ($n = 30$) received 0.25% bupivacaine and 100 mg tramadol to a total volume of 20 mL by the IA route after surgery. Postoperative pain scores were measured on a VAS, at rest and on mobilization at 0.5, 1, 2, 4, 6, 8, 12, and 24 h. Duration of analgesia, the subsequent 24 h consumption of rescue analgesia, time to ambulation, and time to discharge were evaluated. In addition, the systemic side effects of the IA injected drugs were also assessed.

RESULTS: The results showed significantly lower VAS pain scores in group BT ($P \ll 0.1$) when compared with groups T and B. Group BT had a later onset of postsurgical pain and longer time to first rescue analgesic than groups B and T. The 24 h consumption of analgesic was significantly less in group BT when compared with the other two groups (26.7% of the patients required rescue analgesia in group BT, whereas this number was 90% in group B and 86.7% in group T). In addition, time in hours to discharge and time to unassisted ambulation were significantly shorter in group BT when compared with groups T and B, and this was not associated with any detectable systemic effects.

CONCLUSION: The IA admixture of tramadol 100 mg with bupivacaine 0.25% provides a pronounced prolongation of analgesia compared with either drug alone in patients undergoing day care arthroscopic knee surgery.

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Arthroscopic knee surgery is commonly performed as an outpatient procedure and is often associated with postoperative pain. Intraarticular (IA) local anesthetics (LA) are often used for prevention of pain after arthroscopic knee surgery; however, the degree of postoperative pain varies. In an effort to find the ideal regime for sufficient, long-lasting postoperative analgesia, many different drugs, including opioids, nonsteroidal antiinflammatory drugs, ketamine, clonidine, and neostigmine, have been added to the IA LAs.[1–4] The analgesic effect of IA tramadol after arthroscopic knee surgery has been reported recently by Alagol et al.,[5] who reported that IA tramadol 100 mg without LA provided a longer alternative analgesic effect than after IV injection of the same dose of tramadol. However, the IA combination of LA and tramadol had not been evaluated in outpatients undergoing arthroscopic knee surgery.

The primary aim of this study was to compare the analgesic effect of IA bupivacaine 0.25% and tramadol 100 mg, used separately, and evaluate if their combination would provide superior analgesia to each drug alone, as assessed by the Visual Analog pain Scores at rest (VASr) and on mobilization (VASm). The secondary end-points were duration of analgesia, as defined

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by first demand for analgesia (1 g of oral paracetamol), and subsequent 24-h consumption. The time of unassisted ambulation, time to discharge, and side effects were also assessed.

METHODS

After IRB approval and informed written consents, 90 unpremedicated patients scheduled to undergo elective arthroscopic surgery by a single surgeon were included in this prospective, randomized, double-blind study. Patients eligible for participation were older than 18 yr, and were ASA physical status I or II. Patients excluded were those treated with narcotics preoperatively and those who had a contraindication to the use of bupivacaine or tramadol.

Before the operation, all patients received instructions for using a 100-mm VAS score (with 0 = no pain, to 100 = the worst imaginable pain). The baseline pain scores were recorded postoperatively. Pain was assessed by a single interviewer who was not aware of the study medication. Anesthesia was induced with propofol (2.5 mg/kg), rocuronium (0.6 mg/kg) and fentanyl (0.002 mg/kg) and maintained with nitrous oxide 60% in oxygen and sevoflurane. No other supplementary analgesic medication was given during the operation after the first dose of fentanyl. During anesthesia, controlled ventilation was performed via an endotracheal tube. Before surgical incision, a thigh pneumatic tourniquet on the same side as the surgery, at a pressure of 300 mm Hg, was applied to all patients. The same surgeon performed all surgical procedures using a standard surgical technique.

At the end of the operation, patients were allocated, using a randomized number table, into 1 of 3 groups, consisting of 30 patients each. Group T received 100 mg of IA tramadol, group B received 0.25% bupivacaine, and group BT received a mixture of 0.25% bupivacaine and tramadol 100 mg. The volume of the injectate was standardized at 20 mL. The study solution, supplied in a coded syringe, was injected by the surgeon into the knee joint through an arthroscope at the end of surgery, 10 min before tourniquet release.

After the end of anesthesia, patients were transferred to the postanesthesia care unit. Arrival at the postanesthesia care unit was recorded as time zero. The VAS was assessed at predetermined intervals after surgery (0.5, 1, 2, 4, 6, 8, 12, and 24 h). At each time of measurement, pain scoring was performed at rest (VASr) and on mobilization (VASm) (bending of the operated knee). When patients complained of pain (VAS score more than 40), they were given 1 g of paracetamol orally as a rescue medication. Duration of effective analgesia was measured from the time of surgery completion until first requirement of rescue analgesia.

When patients were discharged, they were given a data sheet and they were instructed how to evaluate the degree of pain by using the VAS score ruler. Therefore, they could read by themselves the corresponding numerical score, record it on the data sheet at the predetermined times, and report their analgesic consumption. Also, the patients were asked to record any adverse effect, such as headache, dizziness, somnolence, nausea, and vomiting.

Patients were discharged from the hospital when they were oriented to time and place, were able to void, had stable vital signs, and could ambulate with or without the assistance of crutches. The time of ambulation without any assistance (unassisted ambulation) was the time considered on the data sheet.

All patients were interviewed by the anesthesiologist the day after surgery, to evaluate postoperative pain and adverse effects. The patient-recorded data were subsequently collected.

Statistical analysis

A power analysis considered a change of 30 mm in the VAS score as a significant clinical difference, a standard deviation (SD) of 35 mm was reported in previous studies, a type I error of 5% and a type II error of 10% yielded a sample size of at least 30 patients in each group.

The percentage of patients requiring rescue analgesia in the three groups was compared using the Fisher's exact test. Statistical significance was considered at $P < 0.05$. The analysis of variance with *post hoc* Scheffé test was used to compare the mean ± SD of the VAS pain scores and other continuous data among the three groups. Additionally, to control the assumption of the inter- and intraindividual variability across the VAS observation and its influence on statistical decision making, we also performed a nonparametric analysis of the VAS scores, using nonlinear mixed effect modeling (NONMEM). The model parameters (VAS scores versus time) were estimated using NONMEM version VI (Globomax LLC, Hanover, MD). For the parameters, interindividual variability was modeled using a constant coefficient of variation model,

$$\theta_i = \theta_{TV} \cdot (1 + \eta_i)$$

where θ_i refers to the individual value of the parameter, q_{TV} is the typical value of the parameter, and η is a normally distributed random variable with mean zero and a variance of ω^2. Individual variability is reported as ω, the SD of η in the log domain, which is approximately the coefficient of variation in the standard domain. Residual intraindividual variability was modeled using a standard additive error model,

$$DV_{obs} = DV_{eps} + \epsilon$$

where DV_{obs} refers to the observed dependent variable, and DV_{exp} refers to the predicted dependent variable, ϵ is normally distributed with mean zero and variance σ^2. The objective function for the analysis was −2 log likelihood (−2LL).

Table 1. Demographic and Surgical Data

	Group B (n = 30)	Group T (n = 30)	Group BT (n = 30)
Age (yr)	34.0 ± 11.0	32.9 ± 10.4	36.6 ± 11.6
Weight (kg)	69.6 ± 7.1	68.9 ± 7.5	71.5 ± 7.7
Gender (M/F)	17/13	16/14	15/15
Time of surgery (min)	40.5 ± 7.1	39.0 ± 7.5	41.5 ± 6.9

B = bupivacaine; T = tramadol.

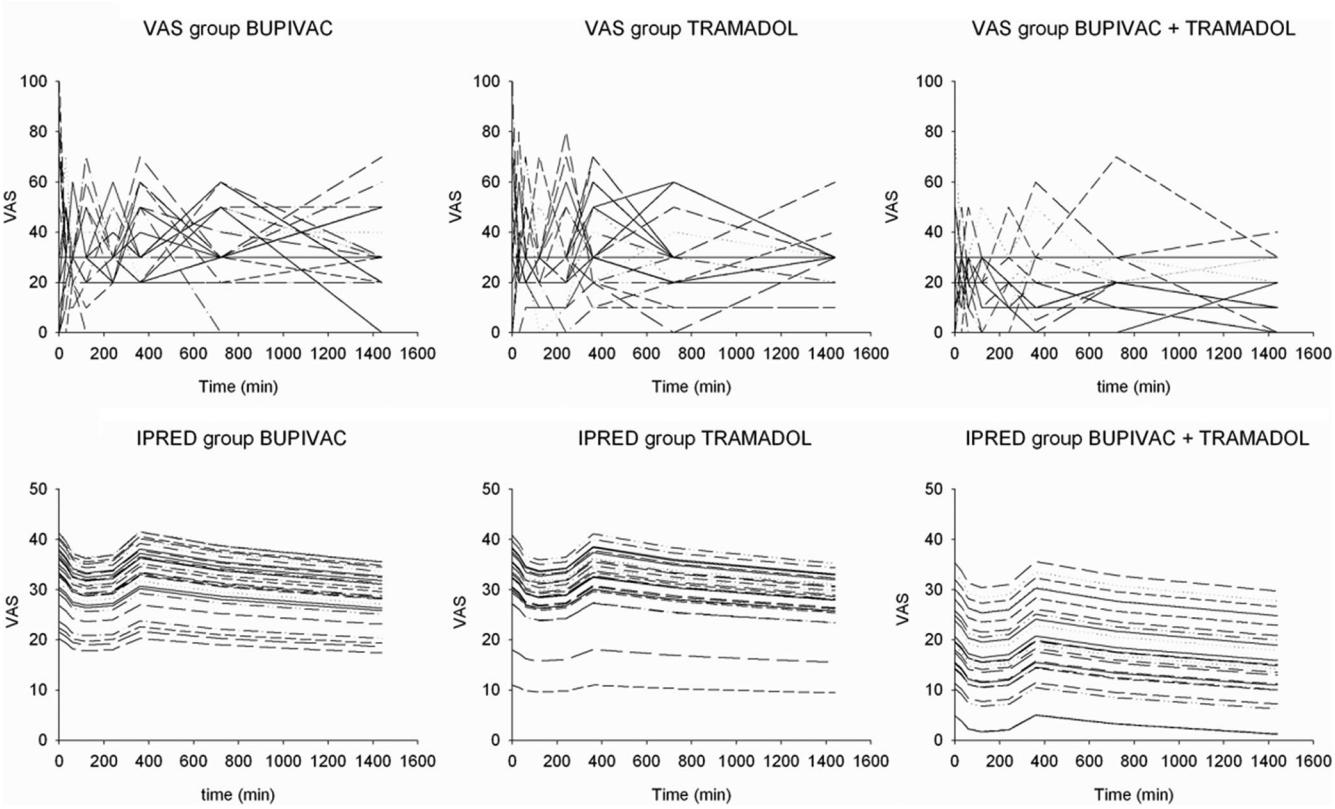

Figure 1. Patient visual analog scores (VAS) at rest: Upper part: Individual measured VAS scores versus time for the three groups. Lower part: Individual (*post hoc*) predicted VAS scores as predicted by NONMEM for each group.

The possible therapeutic effect of tramadol, bupivacaine, or the combination of both drugs on the VAS score was modeled as an additional effect. We first assumed that the underlying model which describes the relationship between the VAS versus time would not be influenced by the drugs used. Therefore, we first estimated the −2LL when no additional effect was present. Thereafter, we estimated the −2LL adding an additional effect on one or more of the therapeutic groups. This additional effect was significantly compared with no effect if the difference in objective function with no effect was more than $P < 0.05$ (χ^2 test) or 3.84 difference in the −2LL adding 1 parameter for nested models. Various models were tested, being group B ≠ group T = group BT; group T ≠ group B = group BT; group B = group T ≠ group BT; and group B ≠ group T ≠ group BT. For the purpose of the analysis, we also assumed a similar additional effect on the VAS at all time points per group. The control file of the final best fitting model can be found in Appendix.

RESULTS

Demographic and surgical data are presented in Table 1. There were no statistically significant differences among the three groups with respect to age, weight, gender, and duration of surgery.

The recorded postoperative VASr and VASm for each patient versus time are plotted in the upper part of Figures 1 and 2, respectively. At all times and for both VASr and VASm, the VAS scores were significantly lower in group BT when compared with groups B and T, as shown in Tables 2 and 3. The additional NONMEM analysis showed a similar result. The best model was found when an additional therapeutic effect was added to group BT, however, without differentiating a separate effect between groups B and T. This final model resulted in a lower −2LL (difference of 39 points) and it was compared with the model without additional effect, which represents a large statistical significance ($P \ll 0.01$) between group BT versus groups B and T. A model predicting a different effect among the three groups did

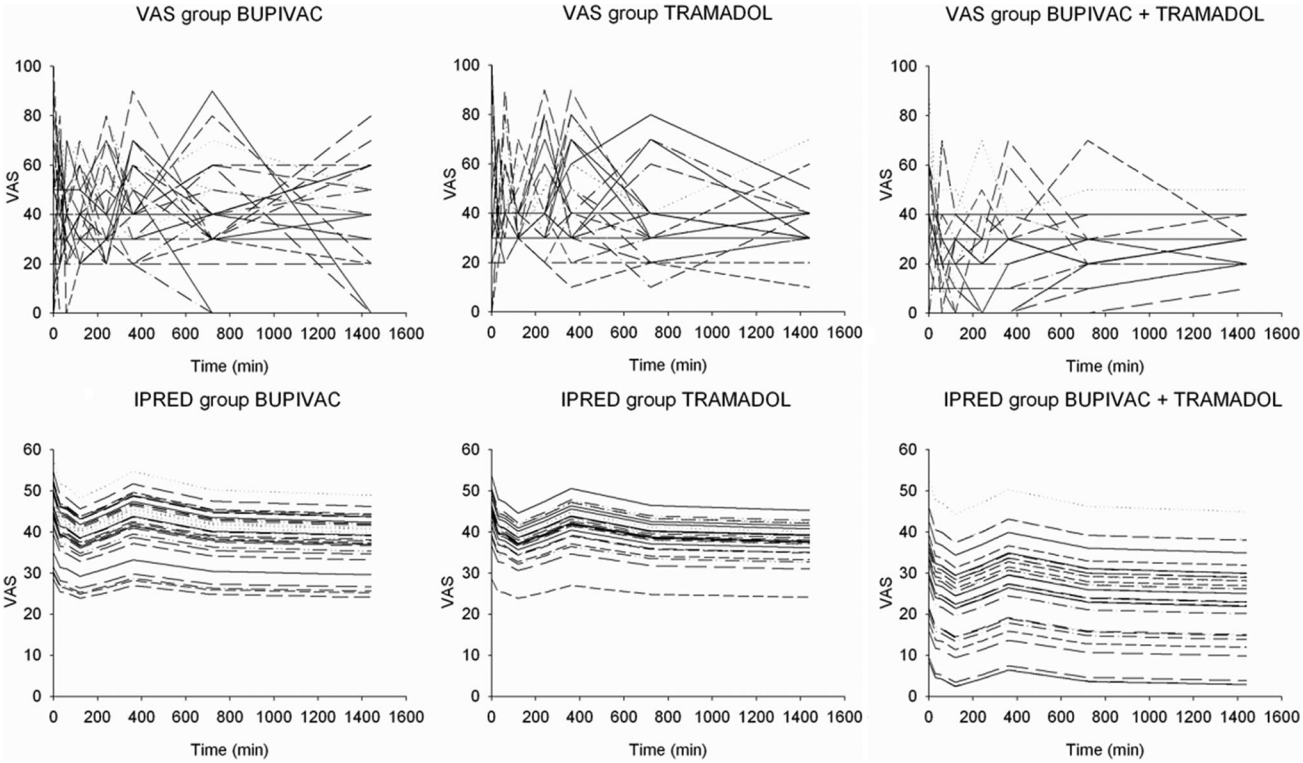

Figure 2. Patient visual analog scores (VAS) during mobilization: Upper part: Individual measured VAS scores versus time for the three groups. Lower part: Individual (*post hoc*) predicted VAS scores as predicted by NONMEM for each group.

Table 2. Visual Analog Scores at Rest (VASr) as Mean ± SD at Different Time Intervals Following Surgeries

	Group B (n = 30)	Group T (n = 30)	Group BT (n = 30)	P (B + T vs B)	P (B + T vs T)
VASr–0 min	32 ± 26	31 ± 23	19 ± 20	0.044	0.042
VASr–30 min	31 ± 13	30 ± 15	18 ± 13	0.003	0.008
VASr–60 min	29 ± 8	28 ± 13	18 ± 14	0.0001	0.005
VASr–2 h	31 ± 14	28 ± 12	16 ± 14	0.0001	0.005
VASr–4 h	31 ± 14	30 ± 18	14 ± 13	0.0001	0.0001
VASr–6 h	34 ± 16	36 ± 19	16 ± 17	0.0001	0.0001
VASr–12 h	35 ± 16	29 ± 16	15 ± 15	0.0001	0.001
VASr–24 h	30 ± 17	29 ± 12	12 ± 13	0.0001	0.0001

B = bupivacaine; T = tramadol.

Table 3. Visual Analog Scores During Motion (VASm) as Mean ± SD at Different Time Intervals Following Surgeries

	Group B (n = 30)	Group T (n = 30)	Group BT (n = 30)	P (B + T vs B)	P (B + T vs T)
VASm–0 min	44 ± 26	43 ± 24	30 ± 22	0.038	0.045
VASm–30 min	41 ± 18	37 ± 11	26 ± 16	0.003	0.01
VASm–60 min	37 ± 16	41 ± 16	24 ± 18	0.013	0.001
VASm–2 h	40 ± 17	36 ± 10	22 ± 15	0.0001	0.0001
VASm–4 h	40 ± 19	42 ± 18	23 ± 17	0.0001	0.0001
VASm–6 h	43 ± 19	45 ± 21	25 ± 17	0.0001	0.0001
VASm–12 h	40 ± 21	38 ± 16	24 ± 14	0.002	0.002
VASm–24 h	36 ± 22	37 ± 11	26 ± 11	0.024	0.0001

B = bupivacaine; T = tramadol.

not result in a better model fit than the final model. The individual predicted VAS scores for each group at rest and during mobilization are shown in Figures 1 and 2D–F. The typical values for both conditions (rest and mobilization) at the various time points are given in Figures 3 and 4. For both conditions, a highly significant difference is seen between the typical values for group BT versus groups B and T. Groups B and T have similar typical values in the model. The interindividual variability analysis resulted in a coefficient of variation of 18%. The beneficial effect of the combined therapy versus single therapy resulted in a typical VAS decrease of 14.3 with a coefficient of variation of 63%. The additive residual intraindividual error was 15.3.

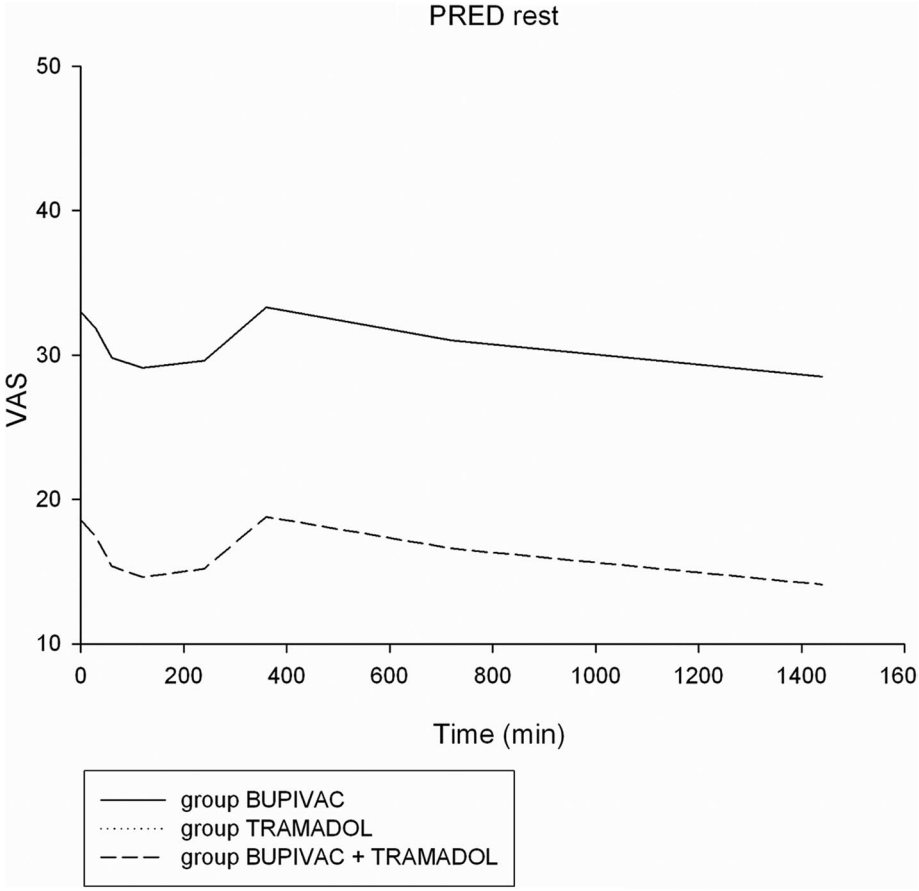

Figure 3. Typical population (*post hoc*) predicted visual analog scores (VAS) for groups B and T (solid line) and group BT (dotted line) at rest.

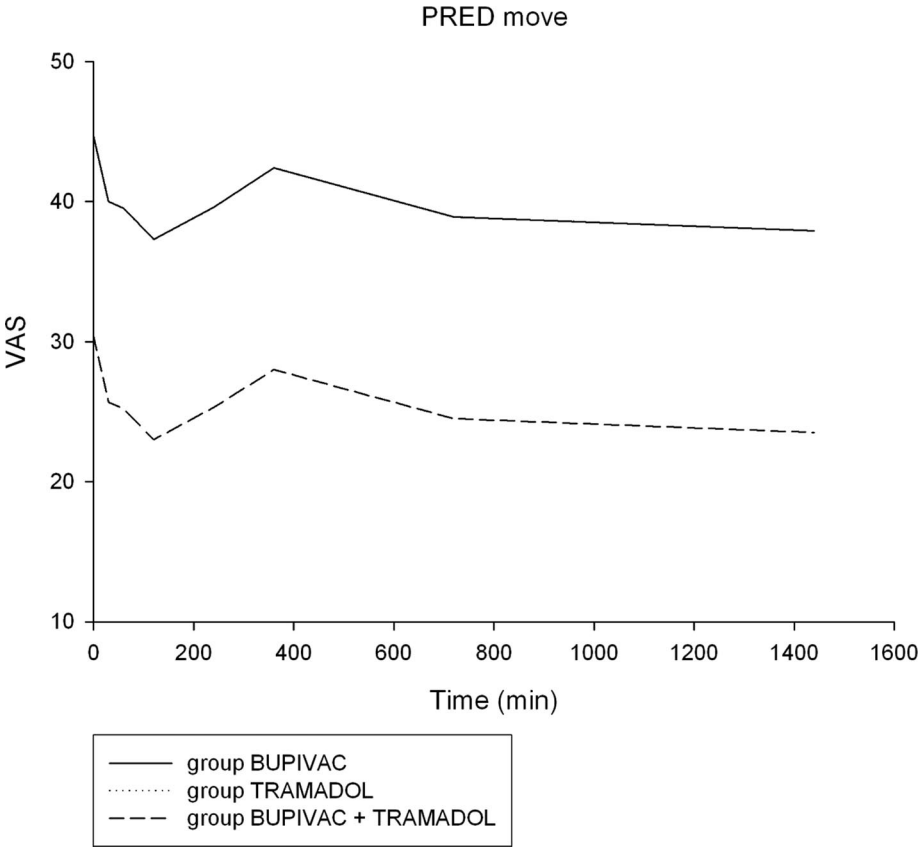

Figure 4. Typical population (*post hoc*) predicted visual analog scores (VAS) for groups B and T (solid line) and group BT (dotted line) during mobilization.

Table 4. Postoperative Quality of Analgesia and Time for Discharge and Ambulation

	Group B ($n = 30$)	Group T ($n = 30$)	Group BT ($n = 30$)	P (B + T vs B)	P (B + T vs T)
No. and % of patients requiring rescue analgesia (Paracetamol)	27 (90%)	26 (86.7%)	8 (26.7%)	0.0001	0.0001
No. of rescue analgesia	1.7 ± 1.0	1.4 ± 0.8	0.4 ± 0.6	0.001	0.001
Total dose (no. of tablets/24 h)	3.3 ± 1.9	2.7 ± 1.6	0.8 ± 1.3	0.001	0.001
Time to discharge (h)	7.5 ± 2.7	7.1 ± 2.4	5.0 ± 1.8	0.001	0.004
Time to ambulation (h)	9.0 ± 4.3	9.2 ± 5.7	4.7 ± 2.1	0.001	0.001

No. = number; % = percentage; B = bupivacaine; T = tramadol.

The percentage of patients in group BT requiring rescue analgesia was 26.7%, which is significantly less than the percentage of patients in either group B (90%) or group T (86.7%). Also, the numbers of rescue analgesia requests as well as the cumulative 24 h analgesic consumption were significantly smaller in group BT compared with groups B or T (Table 4). Subsequently, time to discharge and time to unassisted ambulation were significantly shorter in group BT than in groups B or T (Table 4).

No patient, in any group, showed and/or recorded postoperative headache, nausea, vomiting, dizziness, or somnolence.

DISCUSSION

In the present study, we found lower VAS pain scores, a longer duration of analgesia, and a decrease in the 24 h consumption of rescue analgesia in the group receiving the IA combination of 100 mg tramadol and 0.25% bupivacaine when compared with the groups receiving bupivacaine or tramadol injection alone. There was also earlier recovery of unassisted ambulation and home discharge for the combination group. No side effects were detected in any groups.

Different adjuvant drugs, including opioids, nonsteroidal antiinflammatory drugs, ketamine, clonidine, and neostigmine, have been added to IA LAs to improve the duration and quality of analgesia after knee arthroscopy. A comparative study showed that the most effective drugs administered IA are neostigmine and clonidine when compared with tenoxicam, morphine, and bupivacaine.[1] Evidence indicates that a variety of these drugs have synergistic effects through a local, rather than a central, mechanism.

IA tramadol has also been used for pain management of these patients.[5] Alagol et al.[5] showed that tramadol 100 mg without LA provided lower VAS pain scores and longer analgesic effect after IA administration more than after IV injection of the same doses with no significant side effects.

In our study, IA tramadol had an analgesic effect similar to that of IA bupivacaine. It is possible that the combination of IA tramadol and LA provides its regional analgesic effect by a multimodal mechanism of action, which gives a synergistic effect, as evidenced by the decreased VAS pain scores, decreased need for postoperative analgesics, and an increased analgesic duration, as well as the early unassisted ambulation and discharge.

Although tramadol was initially considered to be a weak μ-opioid agonist, it appears to have multimodal mechanisms of action. It is now accepted that, in addition to the μ-opioid agonist effect, tramadol enhances the function of the spinal descending inhibitory pathway by inhibition of reuptake of both 5-hydroxytryptamine (5-HT) and norepinephrine, together with presynaptic stimulation of 5-HT release.[6,7]

The LA action of tramadol remains unproven. 5-HT3 receptors are expressed on the peripheral and spinal terminals of the nociceptive primary afferent fibers, as well as on the superficial lamina of the dorsal horn, which indicates possible peripheral sites of analgesic action for tramadol.[8,9] Mert et al.[10] have shown a definitive LA effect of tramadol in experiments on frog sciatic nerves. In their animal study, the nerve conduction block of tramadol was 3–6 times weaker than that of lidocaine. Although lidocaine inhibits Na channels, it has been suggested that tramadol inhibits K channels.

Although the analgesic effect of IA opioid with or without LA after arthroscopy is controversial, the existence of agonist-specific IA opioid receptors has been well documented in recent years. Boden et al.[11] found a significant analgesic effect of IA opioid when injected alone and a synergistic effect when added to the LA. It was postulated that peripheral opioid receptors may be activated only in the presence of tissue inflammation. The timing of IA opioid administration may also be an important factor. Whitford et al.[12] found that maintaining tourniquet inflation for 10 min after IA opioid injection improved postoperative analgesia, presumably by allowing tissue binding before tourniquet release, and the subsequent posttourniquet hyperemia and tissue washout.

Furthermore, several publications reported that tramadol, when added to LA, modifies peripheral anesthesia.[13,14] Kapral et al.[13] reported that tramadol increased the duration of analgesia when added to mepivacaine for axillary plexus blockade.

For ethical reasons, we did not include a control group receiving IA placebo and parenteral tramadol, since it has been reported that tramadol provided a

longer analgesic effect after IA administration than after IV injection of the same doses.[5]

Headache, nausea, vomiting, dizziness, and somnolence had been major side effects of IV tramadol when used for postoperative analgesia.[15] The incidence of nausea and vomiting seems to be related mainly to the peak serum concentrations reached by a direct IV loading dose, which causes more symptoms than a subsequent infusion or local infiltration.[16,17] This may partially explain the absence of side effects after the IA tramadol administration in our patients.

In conclusion, our report showed that the IA admixture of 100 mg tramadol with 0.25% bupivacaine decreased both VASr and VASm and provided longer postoperative analgesia than that produced by IA injection of either bupivacaine or tramadol alone. This was also associated with earlier recovery of unassisted ambulation and home discharge. Also, the IA combination of tramadol-bupivacaine was not associated with any side effects.

APPENDIX

```
$PROB Intraartic_tramadol_Bupivac
$DATA DATA_REST.txt
$INPUT ID TIME POD VAS=DV TRT
$PRED
IF (POD.EQ.0) THEN
   TY=THETA(1)*(1+ETA(1))
ENDIF
IF (POD.EQ.30) THEN
   TY=THETA(2)*(1+ETA(1))
ENDIF
IF (POD.EQ.60) THEN
   TY=THETA(3)*(1+ETA(1))
ENDIF
IF (POD.EQ.120) THEN
   TY=THETA(4)*(1+ETA(1))
ENDIF
IF (POD.EQ.240) THEN
   TY=THETA(5)*(1+ETA(1))
ENDIF
IF (POD.EQ.360) THEN
   TY=THETA(6)*(1+ETA(1))
ENDIF
IF (POD.EQ.720) THEN
   TY=THETA(7)*(1+ETA(1))
ENDIF
IF (POD.EQ.1440) THEN
   TY=THETA(8)*(1+ETA(1))
ENDIF
   IF (TRT.EQ.1) THEN
   LESS=0
ENDIF
IF (TRT.EQ.2) THEN
   LESS=0
ENDIF
IF (TRT.EQ.3) THEN
   LESS=THETA(9)*(1+ETA(2))
ENDIF
IPRED=TY-LESS
Y=IPRED+EPS(1)
$THETA
(0, 20, 100); Theta 01
(0, 32, 100); Theta 02
(0, 26, 100); Theta 03
(0, 23, 100); Theta 04
(0, 19, 100); Theta 05
(0, 7, 100); Theta 06
(0, 20, 100); Theta 07
(0, 20, 100); Theta 08
−0.1; Theta 9
$OMEGA 0.01 0.01; Between subject variability
$SIGMA 50; Residual variability
$ESTIMATION MAX=1000 PRINT=1 NOABORT
   METHOD=1 SIG=3
$TABLE ID TIME POD VAS TRT IPRED
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ERRATUM

In the article "Electrical Nerve Stimulation or Ultrasound Guidance for Lateral Sagittal Infraclavicular Blocks: A Randomized, Controlled, Observer-Blinded, Comparative Study" which appeared in the June 2008 issue of volume 106 of *Anesthesia & Analgesia* on pages 1910–5, there was as a copyediting error concerning the needle position of ultrasound guided blocks (Methods, page 1911, first column, last line). It is stated that "the needle was placed in 9 o'clock position." It should be "the needle was placed in 8 o'clock position."

This error has been corrected in the online version of the article available at www.anesthesia-analgesia.org.

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