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Research Article

Role of ketamine and tramadol as adjuncts to bupivacaine 0.5% in paravertebral block for breast surgery: A randomized double-blind study

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KEYWORDS

Paravertebral block;
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Abstract *Background:* Use of adjuncts to local anesthetics is believed to enhance the quality and duration of the peripheral nerve blocks. We tested the hypothesis that addition of ketamine or tramadol to bupivacaine 0.5% in PVB for patients undergoing modified radical mastectomy would enhance postoperative analgesia.

Methods: We prospectively randomized 60 ASA I–III women into three groups: group B (n = 20) who received PVB using plain bupivacaine 0.5% (control group), group K (n = 21) who received ketamine (0.5 mg kg^{-1}) added to bupivacaine 0.5%, and group T (n = 19) who received tramadol (1.5 mg kg^{-1}) added to bupivacaine 0.5%. All the patients were then given a standardized general anesthesia. Primary outcome was the cumulative fentanyl dose given through patient-controlled analgesia (PCA) device in the first 24 h after surgery. Secondary outcomes included dose of fentanyl in the postanesthesia care unit (PACU), time to first dose of fentanyl, and visual analogue scale (VAS) pain scores in PACU and ward.

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Results: The three groups were found to be similar in the cumulative dose of PCA fentanyl in the first 24 h ($P = 0.62$). They were also similar in terms of doses of fentanyl used in PACU ($P = 0.87$), time to first dose of fentanyl requested ($P = 0.57$), and VAS pain scores at all time points ($P > 0.05$).
Conclusion: We concluded that addition of ketamine (0.5 mg kg^{-1}) or tramadol (1.5 mg kg^{-1}) to bupivacaine 0.5% in PVB for modified radical mastectomy do not have any analgesia-enhancing effect.

1. Introduction

Previous studies showed that breast surgery patients receiving thoracic paravertebral block (TPVB) in addition to general anesthesia or intravenous sedation, seem to have shorter recovery times [1], require fewer analgesics [1,2], experience less postoperative pain [2,3], and experience less postoperative nausea and vomiting (PONV) [2,3] compared to patients receiving general anesthesia without TPVB. The increasing popularity of TPVB analgesia as an effective method of intra- and postoperative pain relief for breast surgery [1] warrants more research on combinations of local anesthetics and adjunctive analgesics. Traditionally, perineural infiltration of intercostal nerves is associated with high and rapid absorption of local anesthetic into the systemic circulation, leading to high blood concentrations' [4]. The addition of adjuncts, such as morphine [5], clonidine [6], and neostigmine [7] has been shown to enhance the quality and duration of sensory neural blockade and decrease the dose of local anesthetic and supplemental analgesia. Ketamine has local-anesthetic-like effects [8] and has been extensively used through epidural and caudal routes with variable results [9–12]. Tramadol has also been used as an adjunctive analgesic to local anesthetic in neuraxial and peripheral nerve blocks [13–16]. There is very little research on the efficacy and tolerability of the addition of adjuncts in PVBs [17,18]. The use of tramadol and ketamine as adjuncts in TPVB has not yet been investigated.

Therefore, the objective of the present prospective, randomized, double-blind study was to examine if the addition of ketamine or tramadol to bupivacaine in TPVB would enhance postoperative analgesia after modified radical mastectomy.

2. Methods

After Local Ethics Committee approval, 60 ASA status I–III female patients scheduled to undergo elective modified radical mastectomy were enrolled after giving written consent. The enrollment period lasted from April 2007 to July 2008 in King Faisal Specialist Hospital and Research Center in Riyadh. Exclusion criteria included bleeding disorders, contraindications to nonsteroidal anti-inflammatory drugs (NSAIDs), allergy to amide-type local anesthetics, infection at the thoracic paravertebral injection site, severe spine deformity, pregnancy or breast-feeding, and severe obesity (body mass index >35 kg m^{-2}). At the preoperative visit, the patients were instructed by one of the investigators how to use the visual analogue scale (VAS; 0–10 point where 0 = no pain and 10 = worst imaginable pain) for measurement of pain and how to use the patient-controlled analgesia (PCA) device. All patients received midazolam premedication 5–10 mg PO 15–20 min before surgery and 1 mg granisetron IV as a prophylactic anti-emetic. Clinical monitoring included electrocardiography, pulse oximetry and non-invasive arterial blood pressure. They were randomly divided into three equal groups using computerized randomization tables. A pharmacist who was not involved in the study prepared and released the blinded study local anesthetic medication immediately before the operation. Group B (control group) received plain bupivacaine 0.5% 2 mg kg^{-1} (max 150 mg), group K received bupivacaine as group B plus ketamine 0.5 mg kg^{-1} and group T received bupivacaine as group B plus tramadol 1.5 mg kg^{-1} (max 150 mg). Thoracic paravertebral blocks were applied inside the operating room while in patients in sitting position at levels of T1 (1/3 of the dose) and T4 (2/3 of the dose) by using 22 G Touhy needle according to the approach described by Eason and Wyatt [19] after local infiltration of the skin and subcutaneous tissue of entry site with lidocaine 1% 2–3 ml using 25 G needle. Midazolam 1–2 mg IV was given if needed during the block. All patients then received a general anesthetic without testing the sensory level attained by the TPVB. Intravenous induction was achieved by propofol 2–3 mg kg^{-1} and fentanyl 2–3 mcg kg^{-1}. Endotracheal intubation was facilitated by IV rocuronium 0.6 mg kg^{-1}. Anesthesia was maintained with sevoflurane 2–3% and 40% oxygen in air to maintain normocarbi as monitored by capnography. Heart rate (HR) and mean arterial blood pressure (MBP) were maintained within ±20% of the preoperative baseline by giving IV bolus doses of fentanyl 1–2 μg kg^{-1} if the MAP and heart rate increased more than 20% from the baseline for more than 5 min (where inadequate paravertebral block was suspected). Ephedrine 5 mg was given in IV increments as needed to treat hypotension. By the conclusion of surgery, rocuronium effect was antagonized by IV neostigmine 50 mcg kg^{-1} (max 5 mg) with glycopyrrolate 6 mcg kg^{-1}. After emerging from anesthesia, the patients were transferred to the post-anesthesia care unit (PACU) for a 2-h observation period. Analgesia in the PACU was provided by fentanyl 0.25–0.50 mcg kg^{-1} IV as a rescue medication, if needed, every 10 min until pain VAS score was $\leqslant 3$. Postoperative patient controlled fentanyl analgesia (PCA) was used according to the hospital protocol (20 mcg per bolus dose with a 6-min delay). All patients were given oral acetaminophen 1 g three times daily and ibuprofen 400–600 mg three times daily PO in the surgical ward. Pain intensity on the VAS (0–10) was assessed by nurse staff who were blinded to group allocation at the following times: on admission to PACU, 1 h later, on discharge from the PACU, 4-, 8-, 12-, 18-, and 24-h postoperatively. Incidence of postoperative nausea and vomiting was reported. Metoclopramide (10 mg IV) was given 8-hourly as needed. Time to first using the fentanyl PCA analgesia was recorded and total dose of PCA fentanyl was calculated. Any psychomimetic change (defined as agitation, hallucinations, or vivid dreams) which happened in the PACU or the surgical ward was reported. The patients and the investigators

collecting data were blinded to the group allocation and the composition of the study mixture.

The primary outcome of the study was consumption of PCA fentanyl. From our previous work, we found that patients undergoing breast surgery under combined general anesthesia and PVB required 207 ± 51 mcg (mean ± SD) of fentanyl through PCA in the day of surgery (data not published). We assumed that a 30% difference of fentanyl consumption would be clinically significant between groups. A sample size was calculated to be 18 cases for each group to give a power of 90% at a level of 5% significance. We enrolled 20 cases per group to accommodate for dropouts. Secondary outcomes included probability of post-block hypotension, need for ephedrine use, postoperative pain VAS score, dose of fentanyl in PACU, occurrence of psychomimetic changes and incidence of PONV.

Statistical analyses were performed using the SPSS for Windows, version 15 (SPSS Inc., Chicago, IL). Data were first tested for normality by Klomogorov–Smirnov test. Normally distributed continuous data were analyzed by using one-way analysis of variance (ANOVA). Non-normally distributed continuous and ordinal data were analyzed using Kruskall–Wallis test. Categorical data was analyzed by Chi-square or Fisher's exact test as appropriate. The results are presented as mean ± SD, median (range), or number of patients as appropriate. A P value < 0.05 was considered statistically significant.

3. Results

One hundred and twenty-seven patients were found eligible for the study. Forty-one patients met our exclusion criteria and 26 refused participation. Sixty patients were randomized for three groups: group B ($n = 20$), group K ($n = 21$), and group T ($n = 19$). No patient was excluded from the study.

The three groups were found to be similar in terms of age, body mass index, ASA classification and duration of surgery and anesthesia (Table 1). Two patients in group B, two patients in group K, and one patient in group T showed evidence of block failure (increased blood pressure and heart rate in response to surgical stimulation). Those five patients needed frequent boluses of IV fentanyl to achieve analgesia intraoperatively and in PACU.

The fentanyl dose needed in the PACU and the cumulative fentanyl PCA dose in the day of surgery were similar between the three groups (Table 2). The time interval (h) to request postoperative analgesia [median (range)] was also similar between the three groups [group B 14.5 (0.25–21), group K 14.5 (0.5–18), and group T 13.5 (0.25–19), $P = 0.57$].

Table 1 Patient and procedure characteristics. Data are mean (SD) or median (range).

Variable	Group B ($n = 20$)	Group K ($n = 21$)	Group T ($n = 19$)
Age (years)	49.3 (10.5)	48.2 (8.6)	47.5 (9.3)
Body mass index (kg m^{-2})	29 (2.5)	27.7 (3.2)	27.7 (2.6)
ASA (I/II/III)	4/12/4	5/10/6	4/11/4
Duration of surgery (min)	92.6 (10.7)	93 (8.7)	92.2 (10.1)
Duration of anesthesia (min)	116.6 (11.5)	115.5 (9.6)	118.2 (9.6)

Group B, bupivacaine; group K, ketamine; group T, tramadol.

Table 2 Doses of fentanyl used by patients in PACU and cumulative PCA dose in the first 24 h postoperative. Data are median (range).

Fentanyl dose (mcg)	Group B ($n = 20$)	Group K ($n = 21$)	Group T ($n = 19$)	P value
PACU	0 (0–180)	0 (0–200)	0 (0–200)	0.87
24-h PCA	190 (120–620)	200 (120–700)	180 (120–380)	0.62

PACU, postanesthesia care unit; PCA, patient-controlled analgesia; group B, bupivacaine; group K, ketamine; group T, tramadol.

Table 3 Pain visual analogue score. Data are median (range).

Time	Group B ($n = 20$)	Group K ($n = 21$)	Group T ($n = 19$)	P value
On admission to PACU	1 (0–3)	1 (0–3)	1 (0–3)	0.91
1 h later	1 (0–5)	1 (0–2)	1 (0–5)	0.17
On discharge from PACU	1 (0–3)	2 (0–3)	1 (0–3)	0.08
4-h postoperative	1 (0–4)	1 (0–4)	1 (0–3)	0.88
8-h postoperative	2 (0–5)	2 (0–3)	1 (0–6)	0.19
12-h postoperative	1 (0–3)	1 (0–3)	1 (0–3)	0.96
18-h postoperative	2 (0–5)	2 (1–5)	2 (0–5)	0.91
24-h postoperative	1.5 (0–5)	1 (0–3)	2 (0–3)	0.78

PACU, postanesthesia care unit; group B, bupivacaine; group K, ketamine; group T, tramadol.

Table 4 Complications occurred after block and dose of ephedrine. Data are number (percentage) or median (range).

Variable	Group B ($n = 20$)	Group K ($n = 21$)	Group T ($n = 19$)	P value
Hypotension	3 (15)	3 (14)	4 (21)	0.91
Dose of ephedrine	0 (0–15)	0 (1–15)	0 (0–10)	0.49
PONV	6 (30)	8 (38)	6 (29)	0.84
Antiemetic use	5 (20)	4 (19)	5 (26)	0.66
Psychomimetic changes	0 (0)	4 (19)*	0 (0)	0.02

PONV, postoperative nausea or vomiting; group B, bupivacaine; group K, ketamine; group T, tramadol.
* Significant compared to group B and group T.

There were no statistically significant differences in pain scores between groups at any of the determined eight time points (Table 3).

Untoward effects including episodes of intraoperative hypotension occurring after the PVB, ephedrine use, postoperative nausea and vomiting and antiemetic use were similar in the three groups (Table 4). Four patients in group K showed psychomimetic changes (2 hallucinations and 2 unpleasant dreams). No patient in the study showed any evidence of pneumothorax.

4. Discussion

The major fining of this study was the lack of any analgesia-enhancing effect of ketamine or tramadol added to bupivacaine 0.5% TPVB in females undergoing modified radical mastectomy.

In the last two decades several additives to local anesthetics for regional block have been studied in order to overcome the disadvantages of local anesthetic solutions alone, such as short duration of action and systemic toxicity. To our knowledge, no previous study has investigated the role of ketamine or tramadol as adjuncts to local anesthetics in PVB.

The use of ketamine as an adjunct to local anesthetic has been extensively investigated in epidural route with favorable results [9,11–13] but much less in peripheral nerve blocks with variable results [20,21]. The reason that made the investigators try ketamine as an adjunct to local anesthetics in neuraxial or peripheral nerve blocks is the local anesthetic-like action that ketamine has. Wagner et al. found that ketamine could interact with sodium channel of rat myocyte in a local anesthetic-like fashion [22]. Adding to this effect is the ability of ketamine to block *N*-methyl-D-aspartate receptors which are thought to be found all over the human body nervous system playing a central role in nociception [23]. Weber et al. [24] studied the effect of ketamine on frog nerve conduction and also reported that subcutaneous infiltration of ketamine 0.5% caused loss of painful and thermal sensation in volunteers but the first study that investigated the role of ketamine as an adjunct to local anesthetic in peripheral nerve block has been released in 2002 [20]. In this study, Lee et al. have investigated the sensory and motor effects of ketamine when added to ropivacaine 0.5% in interscalene block. Similar to our results, they did not find any sensory or motor prolonging effect of ketamine. Again they reported 44% incidence of psychomimetic side effects in patients who had received ketamine/ropivacaine in comparison to 5% in those patients who had received ropivacaine alone. We assume three explanations for the lack of postoperative opioid-sparing effect of ketamine in PVB. The first two explanations were underscored by Lee et al. in their study [20]. They stated that the low concentration of ketamine in their study (0.1%) might not be enough to exert its local anesthetic action. They also assumed that the ability of ketamine to exert local antinociception effect is only effective when there is an inflammatory process at the site of injection which is not the case in their or our study. The third explanation we assume is the availability of ketamine at the site of injection. The dose of ketamine we have used (0.5 mg kg^{-1}) might have been absorbed quickly in the systemic circulation and any local anesthetic effect could have been masked specially with the long-acting local anesthetic we used (bupivacaine). This also might have happened in the study of Lee et al. as they injected their study solution in the interscalene area which is vessel-rich. The relatively high incidence of ketamine-related psychomimetic adverse effects in both studies may support this explanation. This also can explain the good analgesia enhancing effect and the lack of psychomimetic effects of ketamine when given in the epidural or caudal route where the systemic absorption is slow.

Tramadol is an analgesic drug that acts at central and peripheral μ-opioid and monoaminergic receptors [25]. Its local anesthetic effects and lack of irreversible nerve toxicity have been shown in an animal study [26]. Tramadol has also some affinity to peripheral α-2 receptors which may explain its analgesic effect when given in the vicinity of peripheral nerves [27]. Tramadol was found to be as effective as lidocaine when injected subcutaneously in patients undergoing superficial minor procedures [28]. As the case with ketamine, tramadol has been shown to be a useful adjunct to local anesthetics when given neuraxially [13,14,16] but its analgesia-enhancing effect is very variable when used in peripheral nerve blocks. Some studies showed a beneficial effect [29–31] and others showed no benefit [32,33].

Our results are similar to the results of previous two studies which use tramadol as adjuncts to local anesthetics [32,33]. In the first study, Mannion et al. [32] added tramadol 1.5 mg kg^{-1} to levobupivacaine 0.5% (0.4 ml kg^{-1}) in psoas compartment block for patients undergoing primary total hip or knee replacement and they did not find any benefit in comparison to plain levobupivacaine. In the other study, Kesimci et al. [33] added tramadol 100 mg to ropivacaine 0.75% in axillary brachial plexus block for patients undergoing hand or forearm surgery and they did not find any analgesia-enhancing effect for tramadol in comparison to plain ropivacaine.

On the other hand, three studies showed a beneficial effect for tramadol as an adjunct to local anesthetics. In the first study, Kapral et al. [29] demonstrated that the addition of tramadol 100 mg to mepivacaine 1% for axillary brachial plexus block significantly prolonged sensory and motor block compared with plain mepivacaine or axillary block with intravenous tramadol. In the second study, Robaux et al. [30], studied the effect of addition of 3 different doses of tramadol (40, 100 and 200 mg) to mepivacaine 1.5% in axillary brachial plexus block. They found that addition of tramadol enhances in a dose-dependent manner the duration of postoperative analgesia compared to plain mepivacaine. In the third study, Kaabachi et al. [31] found that the addition of tramadol (100 or 200 mg) to lidocaine 1.5% for axillary brachial plexus block significantly prolonged postoperative pain-free periods compared to plain lidocaine.

Comparison of these studies is difficult because of the versatility of the used local anesthetics, dose of tramadol, type of surgery, and the site of nerve blocks. We observe in these different studies that tramadol always shows its analgesia-enhancing effect when combined with short-acting local anesthetics (mepivacaine and lidocaine) but not with long-acting local anesthetics (levobupivacaine and ropivacaine). That may explain the lack of its favorable effect in our study as we used the long-acting local anesthetic bupivacaine which may have masked a possible analgesic effect of tramadol. All the beneficial effects of tramadol have been shown in axillary brachial plexus block. A difference in neural structure between these peripheral nerves and the more central spinal nerves in PVB may explain the susceptibility to the local-anesthetic effect of tramadol. The dose of tramadol we added (1.5 mg kg^{-1}) may not be high enough to exert any analgesic effect. We could not use a higher dose of tramadol (200 mg) as in some previous studies [31] because of the possibility of epidural and intrathecal injections in PVB.

Hypotension that occurred after the PVB in about 20% of patients can be explained by unilateral sympathectomy that may follow instillation of local anesthetics near the thoracic sympathetic ganglia [34]. Use of prophylactic antiemetic (granisetron) and induction of general anesthesia with propofol may decrease the incidence of PONV in all patients. Use of prophylactic antiemetic in this type of surgery is recommended due to the high incidence of PONV [35].

We conclude that addition of ketamine (0.5 mg kg^{-1}) or tramadol (1.5 mg kg^{-1}) to bupivacaine 0.5% in PVB for female patients undergoing modified radical mastectomy does not have any analgesia-enhancing effect in the postoperative period as regards to VAS or 24-h fentanyl consumption. On

the contrary, ketamine addition causes a harmful effect by producing psychomimetic changes.

References

[1] Terheggen MA, Wille F, Borel IH, Ionescu TI, Knape JT. Paravertebral blockade for minor breast surgery. Anesth Analg 2002;94:355–9.

[2] Pusch F, Freitag H, Weinstabl C, Obwegeser R, Huber E, Wilding E. Single-injection paravertebral block compared to general anaesthesia in breast surgery. Acta Anaesthesiol Scand 1999;43:770–4.

[3] Klein SM, Bergh A, Steele SM, Georgiade GS, Greengrass RA. Thoracic paravertebral block for breast surgery. Anesth Analg 2000;90:1402–5.

[4] Tuker GT, Moore DC, Brindenbaugh PO, Brindenbaugh LD, Thomson GE. Systemic absorption of mepivacaine in commonly used regional block procedures. Anesthesiology 1972;37:277–87.

[5] Reuben SS, Reuben JP. Brachial plexus anesthesia with verapamil and/or morphine. Anesth Analg 2000;91:379–83.

[6] Ivani G, de Negri P, Conio A, Amati M, Roero S, Giannone S, et al. Ropivacaine–clonidine combination for caudal blockade in children. Acta Anaesthesiol Scand 2000;44:446–9.

[7] Memis D, Turan A, Karamanlioglu B, Kaya G, Sut N, Pamukcu Z. Caudal neostigmine for postoperative analgesia in paediatric surgery. Paediatr Anaesth 2003;13:324–8.

[8] Dowdy EG, Kaya K, Gocho Y. Some pharmacologic similarities of ketamine, lidocaine, and procaine. Anesth Analg 1973;52:839–42.

[9] Tan P-H, Kuo M-C, Kao P-F, Chia Y-Y, Liu K. Patient controlled epidural analgesia with morphine and morphine-plus ketamine for post-operative pain relief. Eur J Anaesthesiol 1999;16:820–5.

[10] Taura P, Fuster J, Blasi A, Martinez-Ocon J, Anglada T, Beltran J, et al. Postoperative pain relief after hepatic resection in cirrhotic patients: the efficacy of a single small dose of ketamine plus morphine epidurally. Anesth Analg 2003;96:475–80.

[11] Wong CS, Liaw WJ, Tung CS, Su YF, Ho ST. Ketamine potentiates analgesic effect of morphine in postoperative epidural pain control. Reg Anesth 1996;21:534–41.

[12] Weir PS, Fee JP. Double-blind comparison of extradural block with three bupivacaine–ketamine mixtures in knee arthroplasty. Br J Anaesth 1998;80:299–301.

[13] Baraka A, Jabbour S, Ghabash M, Nader A, Khoury G, Sibai A. A comparison of epidural tramadol and epidural morphine for postoperative analgesia. Can J Anesth 1993:308–13.

[14] Delilkan AE, Vijayan R. Epidural tramadol for postoperative pain relief. Anaesthesia 1993;48:328–31.

[15] Alhashemi JA, Kaki AM. Effect of intrathecal tramadol administration on postoperative pain after transurethral resection of prostate. Br J Anaesth 2003;91:536–40.

[16] Murthy BVS, Pandya KS, Booker PD, Murray A, Lintz W, Terlinden R. Pharmacokinetics of tramadol in children after i.v. or caudal epidural administration. Br J Anaesth 2000;84:346–9.

[17] Burlacu CL, Frizelle HP, Moriarty DC, Buggy DJ. Fentanyl and clonidine as adjunctive analgesics with levobupivacaine in paravertebral analgesia for breast surgery. Anaesthesia 2006;61:932–7.

[18] Burlacu CL, Frizelle HP, Moriarty DC, Buggy DJ. Pharmacokinetics of levobupivacaine, fentanyl, and clonidine after administration in thoracic paravertebral analgesia. Reg Anesth Pain Med 2007;32:136–45.

[19] Eason MJ, Wyatt R. Paravertebral thoracic block: a reappraisal. Anaesthesia 1979;34:638–42.

[20] Lee IO, Kim WK, Kong MH, Lee MK, Kim NS, Choi YS, et al. No enhancement of sensory and motor by ketamine added to ropivacaine interscalene brachial plexus blockade. Acta Anaesthesiol Scand 2002;46:821–6.

[21] Meurant F, Colling E, Welter J, Koch JP, Merle M. Effect of clonidine, tramadol, and s(+) ketamine as adjuvants in brachial plexus anesthesia using ropivacaine versus levobupivacaine. Can J Anesth 2006;53:2413–7.

[22] Wagner LE, Gingrich KJ, Kulli JC, Yang J. Ketamine blockade of voltage-gated sodium channels, evidence for a shared receptor site with local anesthetics. Anesthesiology 2001;95:1406–13.

[23] Coggeshall RE, Carlton SM. Receptor localization in the mammalian dorsal horn and primary afferent neurons. Brain Res Rev 1997;24:28–66.

[24] Weber WV, Jawalekar KS, Jawalekar SR. The effect of ketamine on the nerve conduction in isolated sciatic nerves of the toad. Neurosci Lett 1975;1:115–20.

[25] Budd K, Longford R. Tramadol revisited. Br J Anaesth 1999;82:493–5.

[26] Tsai YC, Chang PJ, Jou IM. Direct tramadol application on sciatic nerve inhibits spinal somatosensory evoked potentials in rats. Anesth Analg 2001;92:1547–51.

[27] Kayser V, Besson JM, Guilbaud G. Evidence for noradrenergic component in the antinociceptive effect of the analgesic agent tramadol in an animal model of clinical pain. Eur J Pharmacol 1992;224:83–8.

[28] Altunkaya H, Ozer Y, Kargi E, Ozkocak I, Hosnuter M, Demirel CB, et al. The postoperative analgesic effect of tramadol when used as subcutaneous local anesthetic. Anesth Analg 2004;99:1461–6.

[29] Kapral S, Golmann G, Woltl B. Tramadol added to mepivacaine prolonged the duration of an axillary brachial plexus blockade. Anesth Analg 1999;88:853–6.

[30] Robaux S, Blunt C, Viel E, Cuvillon Ph, Nouguier Ph, Dautel G, et al. Tramadol added to 1.5% mepivacaine for axillary brachial plexus block improves postoperative analgesia dose-dependently. Anesth Analg 2004;98:1172–7.

[31] Kaabachi O, Ouezini R, Koubaa W, Ghrab B, Zargouni A, Abdelaziz A. Tramadol as adjuvant to lidocaine for axillary brachial plexus block. Anesth Analg 2009;108:367–70.

[32] Mannion SO, Callaghan S, Murphy DB, Shorten GD. Tramadol as adjunct to psoas compartment block with levobupivacaine 0.5%: a randomized double-blinded study. Br J Anaesth 2005;94:352–6.

[33] Kesimci E, Izdes S, Gozdemir M, Kanbak O. Tramadol does not prolong the effect of ropivacaine 7.5 mg/ml for axillary brachial plexus block. Acta Anaesthesiol Scand 2007;51:736–41.

[34] Karmakar MK. Thoracic paravertebral block. Anesthesiology 2001;95:771–80.

[35] Fujii Y, Toyooka H, Tanaka H. Granisetron–droperidol combination for the prevention of postoperative nausea and vomiting in female patients undergoing breast surgery. Br J Anaesth 1998;81:387–9.