Effect of tramadol as an adjuvant to local anesthetics for brachial plexus block: A systematic review and meta-analysis

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Abstract

Background

Tramadol, a 4-phenyl-piperidine analog of codeine, has a unique action in that it has a central opioidergic, noradrenergic, serotonergic analgesic, and peripheral local anesthetic (LA) effect. Many studies have reported contradictory findings regarding the peripheral analgesic effect of tramadol as an adjuvant to LA in brachial plexus block (BPB). This meta-analysis aimed to evaluate the effects of tramadol as an adjunct to LA in BPB during shoulder or upper extremity surgery.

Methods

We searched the PubMed, EMBASE, Cochrane, KoreaMed databases, and Google Scholar for eligible randomized controlled trials (RCTs) that compared BPB with LA alone and BPB with LA and tramadol. Primary outcomes were the effects of tramadol as an adjuvant on duration of sensory block, motor block, and analgesia. Secondary outcomes were the effects of tramadol as an adjuvant on time to onset of sensory block and motor block and on adverse effects. We performed the meta-analysis using Review Manager 5.3 software.

Results

We identified 16 RCTs with 751 patients. BPB with tramadol prolonged the duration of sensory block (mean difference [MD], -61.5 min; 95% CI, -95.5 to -27.6; \(P = 0.0004\)), motor block (MD, -65.6 min; 95% CI, -101.5 to -29.7; \(P = 0.0003\)), and analgesia (MD, -125.5 min; 95% CI, -175.8 to -75.3; \(P < 0.0001\)) compared with BPB without tramadol. Tramadol also shortened the time to onset of sensory block (MD, 2.1 min; 95% CI, 1.1 to 3.1; \(P < 0.0001\)) and motor block (MD, 1.2 min; 95% CI, 0.2 to 2.1; \(P = 0.010\)). In subgroup analysis, the duration of sensory block, motor block, and analgesia was prolonged for BPB with tramadol 100 mg (\(P < 0.05\)) but not for BPB with tramadol 50 mg. The quality of evidence was high for duration of analgesia according to the GRADE system. Adverse effects were comparable between the studies.
Conclusions
In upper extremity surgery performed under BPB, use of tramadol 100 mg as an adjuvant to LA appears to prolong the duration of sensory block, motor block, and analgesia, and shorten the time to onset of sensory and motor blocks without altering adverse effects.

Introduction
A brachial plexus block (BPB) provides anesthesia and analgesia during surgery involving the upper limb and for acutely painful conditions, and is the most frequent plexus block performed by anesthesiologists. It is worthwhile to explore the options for extending pain relief while minimizing the adverse effects of local anesthesia. Local anesthetics (LAs) have been used with various perineural adjuvants, including dexamethasone [1, 2], clonidine [3], dexmedetomidine [4], opioids [5], and magnesium [6], to enhance the quality and duration of anesthesia and postoperative analgesia.

Systemic opioids have been used to relieve pain during surgery for many years, but the effects of perineural opioid adjuvants on BPB are controversial. Some studies have reported that addition of opioids such as fentanyl, alfentanil, morphine, buprenorphine, and meperidine to BPB improves sensory block, motor block, and analgesia, but other studies have found no such effect [7–9].

Tramadol administered parenterally or orally has proven effective in managing acute postoperative pain in adults [10]. Tramadol is a unique opioid with two modes of action for inhibition of pain, i.e., an opioid action mediated by the μ receptor and a non-opioid action mediated by α2-adrenergic and serotoninergic activity [11, 12]. The monoaminergic activity of tramadol inhibits the descending pain pathways, resulting in suppression of nociceptive transmission at the spinal level [13]. Tramadol also exhibits LA properties by blocking K+ channels [14]. Clinically, intradermal administration of tramadol provides local anesthesia for minor skin procedures [15]. Many studies have characterized the effects of tramadol as an adjuvant to LA in BPB [16–31]. However, these studies have yielded variable results regarding the analgesia-enhancing effects of tramadol when used in BPB; while some studies showed a beneficial effect, others showed no benefit.

The purpose of this meta-analysis and systematic review was to evaluate the effects of tramadol as an adjunct to LA in BPB for shoulder and upper extremity surgery.

Materials and methods
This meta-analysis of randomized controlled trials (RCTs) evaluated the effect of tramadol as an adjuvant to LA in BPB and was performed according to the recommendations of the PRISMA statement. The systematic review was registered on PROSPERO under the number CRD42015023489.

Literature search
Following the protocol recommended by the Cochrane Collaboration, we performed a systematic literature search for RCTs to evaluate the effects of tramadol as an adjunct to LA in BPB for shoulder or upper extremity surgery. The PubMed, EMBASE, Cochrane CENTRAL, and
KoreaMed databases as well as Google Scholar were systematically searched for RCTs performed in adults (aged older than 18 y) up to November 2015 without language restrictions. The search strategy comprised the following key words: (“tramadol”) and (“local anesthetic”) and (“axillary block” or “brachial plexus block” or “infraclavicular block” or “interscalene block” or “supraclavicular block”) as outlined in Supporting Information (S1 File).

Study selection
The studies included in this analysis were peer-reviewed RCTs that compared BPB with LA alone and BPB with LA and tramadol for shoulder or upper extremity surgery in adult patients. Review articles, case reports, letters to the editor, commentaries, proceedings, laboratory studies, and other non-relevant studies were excluded. Two authors (JBJ and YKC) independently assessed the articles for compliance with the inclusion/exclusion criteria. Any disagreement was resolved by discussion or consultation with a third independent investigator (HWS).

Data extraction and assessment of outcomes
The primary outcomes were the effects of tramadol as an adjuvant to LA on duration of sensory block, motor block, and analgesia. The secondary outcomes were the effects of tramadol as an adjuvant to LA on time to onset of motor block and sensory block and on the adverse effects of BPB for shoulder and upper extremity surgery.

Using standardized forms, two authors (JBJ and JYP) independently extracted the following data: the name of the first author, year of publication, type of surgery, type and dose of LA, volume of LA, dose of tramadol, number of patients, technique used for nerve guidance (landmark, nerve stimulator, or ultrasound guidance), type of BPB approach (axillary, infraclavicular, interscalene, or supraclavicular), definitions of sensory and motor block (duration of sensory block, duration of motor block, duration of analgesia, onset of sensory block, and onset of motor block), and adverse effects (nausea, vomiting, pruritus, and sedation). In our analysis, there were two studies that contained more than two groups for tramadol as an adjuvant to LA (one by Kabachi et al.[24] that included arms receiving tramadol 100 mg and 200 mg and the other by Robaux et al.[29] that included arms receiving tramadol 40 mg, 100 mg, and 200 mg). Data from RCTs with more than two intervention groups need to be combined into a single group according to the formula for combining groups in the Cochrane Handbook [32]. However, we used only the data for the 50 mg and 100 mg doses in the meta-analysis for comparison of the effects of tramadol according to dose strength. We attempted to contact the authors of studies that had insufficient or missing data. If contact was not possible, we extrapolated data from the study text or tables to obtain the relevant information. Values for the duration and time to onset of sensory or motor block were converted into minutes and the adverse effects of BPB were reported as the number of patients. The control group included patients who received LA alone in BPB and the intervention group included those who received LA with tramadol in BPB during surgery.

Assessment of risk of bias
Two authors (JBJ and YKJ) independently evaluated the quality of the RCTs by using the risk of bias tool in Review Manager (RevMan 5.3, The Cochrane Collaboration, Oxford, UK). Quality was evaluated using the following seven potential sources of bias: random sequence generation, allocation concealment, blinding of the participants, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. The methodology for each RCT was graded as “high,” “low,” or “unclear” to reflect either a high, low, or uncertain risk of bias, respectively.
Statistical analysis

The statistical analysis was performed using RevMan 5.3. We computed the mean difference (MD) with its 95% confidence intervals (CIs) for continuous variables and the relative risk (RR) with corresponding 95% CIs for dichotomous outcome data. The overall data were determined using a Z-test. All reported *P*-values are two-sided. A two-sided *P*-value < 0.05 was considered to be statistically significant. Statistical heterogeneity was estimated using the $I^2$ statistic, which was deemed to be significant when $I^2$ values were above 50%. The Mantel-Haenszel or inverse variance fixed-effects model was used for the study without significant heterogeneity, while the Mantel-Haenszel or inverse variance random-effects model was used for the study with significant heterogeneity. Sensitivity analyses were performed by excluding studies with a high risk of bias.

We performed subgroup analyses for primary outcomes on the basis of type of BPB approach (axillary, infraclavicular, interscalene, or supraclavicular), dose of tramadol (50 mg or 100 mg), type of LA (intermediate-acting LA [lidocaine, mepivacaine, or prilocaine] or long-acting LA [ropivacaine, bupivacaine, or levobupivacaine]), and volume of LA used for BPB (≤30 mL or >30 mL).

If the funnel plot was visually asymmetric or if the *P*-values were < 0.1 on Egger’s linear regression test, the presence of a possible publication bias was suspected. In such cases, a trim-and-fill analysis was performed to confirm publication bias.

Predefined sources of heterogeneity and GRADE guidelines

There was heterogeneity with regard to the definitions of times to onset and duration of sensory block and motor block. Therefore, we assessed the strength of evidence from the RCTs using the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) guidelines. The GRADE tool evaluates the quality across RCTs for each outcome. Based on key elements, including study quality, consistency, directness, precision, and publication bias, the GRADE tool classifies the strength of the synthesized evidence into four categories: high quality (further research is very unlikely to change the confidence in the estimate of effect); moderate quality (further research is likely to have an important impact on the confidence in the estimate of effect); low quality (further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate); and very low quality (there is a high degree of uncertainty about the estimate).

Results

Study search

Our initial electronic search identified 94 potential RCTs (24 from PubMed, 38 from EMBASE, 25 from Cochrane CENTRAL, 3 from KoreaMed, and 4 from Google Scholar). We identified 16 studies [16–31] that used tramadol (50 mg or 100 mg) and were published between 1999 and November 2015. These studies included a total of 751 patients (377 who received LA alone and 374 who received LA with tramadol) (Fig 1). No further records were derived from ClinicalTrials.gov or by contacting authors.

Study characteristics and data

The studies included in this review originated from eight countries, i.e., Austria [31], France [29], Germany [28], India [16, 27], Italy [22, 30], Pakistan [17], Turkey [18, 20, 21, 25, 26], and Tunisia [19, 24]. The patients had undergone various types of surgery, including repair of an arteriovenous fistula [25], carpal tunnel release [29, 30], shoulder arthroplasty [22], and...
shoulder or upper extremity surgery [16–21, 23, 24, 26–28, 31]. There were no studies using an infraclavicular approach for BPB. The details of BPB were recorded according to type of approach (axillary [17, 18, 20, 21, 24–26, 28–31], interscalene [22], supraclavicular [16, 19, 23, 27]), the technique used for nerve guidance (landmark [16, 17, 23, 27, 28], nerve stimulator [18, 20–22, 24–26, 29–31] or ultrasound guidance [19]), type of LA (bupivacaine [16, 27], levobupivacaine [20, 22], lidocaine [19, 24], mepivacaine [29, 31], prilocaine [28], ropivacaine [18, 23, 25, 26, 30], or a mixture of LA agents [17, 21]), dose of tramadol (50 mg [18, 23], 100 mg, or 1.5 mg/kg [16, 17, 19–22, 24–31]), and the definitions of sensory block, motor block, and analgesia in all the studies (Table 1).

Risk of bias assessment
A risk of bias assessment was performed to determine study quality and potential bias. All 16 studies mentioned randomization [16–31], and 15 studies included the details of concealed allocation [16–19, 21–31]. However, five studies were conducted without blinding for assessment of outcomes [17, 23, 25, 30, 31]. One study did not state the details of exclusion in the number in each group [29] and the other study reported selective outcomes [16] (Fig 2).

Publication bias
We evaluated a funnel plot for every comparison and estimated the publication bias using Egger’s linear regression method. Egger’s linear regression method indicated the publication bias for the following comparisons (>10 studies for comparison): duration of sensory block ($P = 0.00985$), duration of motor block ($P = 0.01386$), duration of analgesia ($P = 0.00995$), and
| Reference | Studies | Surgery | Groups | LA volume for BPB | Groups (perineural adjuvant with LA) | Patient age, y | Patients (n) | Characteristics of block |
|-----------|---------|---------|--------|-----------------|-------------------------------|--------------|-------------|--------------------------|
| [16]      | Nagpal 2015 | Forearm bone fracture surgery | 0.5% bupivacaine 18 ml | 28 | Tramadol 100 mg | 20–60 | 30 | Landmark | Supraclavicular |
|           |         |         |        |                 | Tramadol 100 mg (IV) |                     |             | DS–to reappearance of pinprick test using 3-point scale 1, DM–to modified Bromage scale 3, DA–to first rescue analgesic request, OS–to A type pinprick test using 3-point scale 1 (loss of sensation), OM–to modified Bromage scale 0 (motor paralysis of wrist and hand). |
|           |         |         |        |                 | Control |                     |             |            |                          |
| [17]      | Khosa 2015 | Surgery for forearm and hand | 0.5% bupivacaine 20 ml + lidocaine 10 ml with adrenaline | 32 | Tramadol 100 mg | 18–60 | 30 | Landmark | Axillary |
|           |         |         |        |                 | Control |                     |             |             | DS–using pinprick test response, DM–using Modified Bromage scale, DA–to first rescue analgesic request, OS–to pinprick using 3-point scale, OM–to modified Bromage scale. No clear definitions for DS, DM, DA, OS, and OM. |
|           |         |         |        |                 |                      |             |             |                          |
| [18]      | Senel 2014 | Forearm and hand surgery | 0.375% ropivacaine 40 ml | 40 | Tramadol 50 mg | 18–60 | 12 | Nerve stimulator | Axillary |
|           |         |         |        |                 | Control |                     |             |             | Sensory and motor check for 4 nerves (radial, ulnar, median, musculocutaneous nerve). DS–to reappearance of pinprick test using 3-point scale 1, DM–to modified Bromage scale 3, No clear definitions for DA, OS, OM. |
|           |         |         |        |                 | Ketamine 50 mg |                     |             |             |                          |
| [19]      | Trabelsi 2013 | Upper limb surgery | 2% lidocaine 15 ml | 17 | Tramadol 100 mg | 18–80 | 20 | Ultrasound | Supraclavicular |
|           |         |         |        |                 | Control |                     |             |             | DS–to reappearance of pinprick test using 3-point scale 1, DM–to modified Bromage scale 3, DA–to first rescue analgesic request, OS–to B type pinprick test using 3-point scale 2 (loss of sensation to touch), OM–to modified Bromage scale 0. |
|           |         |         |        |                 | Dexamethasone 8 mg |                     |             |            |                          |

(Continued)
| Reference | Studies | Surgery | Groups | LA volume for BPB | Groups (perineural adjuvant with LA) | Patient age, y | Patients (n) | Characteristics of block |
|-----------|---------|---------|--------|------------------|-------------------------------------|---------------|-------------|-------------------------|
| [20]      | Yurtlu 2012 | Hand and forearm surgery | 0.5% levobupivacaine 36 ml | 38 | Tramadol 100 mg | No details given (mean; 36–38) | 28 | 28 | Axillary | Sensory and motor check for 4 nerves (radial, ulnar, median, musculocutaneous nerve). DM—to motor block using 3-point scale 0 (no motor block), DA—to first rescue analgesic request, OS—to loss of sense to B type pinprick using 3-point scale 2 in all 4 nerves, OM—no comment. |
| [21]      | Geze 2012 | Hand, forearm, wrist surgery | 0.25% levobupivacaine 40 ml + lidocaine 40 mg | 40 | Tramadol 100 mg | Nerve stimulator | 18–60 | 20 | Axillary | Sensory and motor check for 4 nerves (radial, ulnar, median, musculocutaneous nerve). DS—to reappearance of sensory block using 3-point scale 0, DM—to motor block using 3-point scale 0, DA—to first rescue analgesic request, OS—to complete sensory block, OM—to motor block using 3-point scale 0. |
| [22]      | Alemano 2012 | Shoulder arthroplasty | 0.5% levobupivacaine 0.4 ml/kg | 24 | Tramadol 1.5 mg/kg | Nerve stimulator | Above 18 | 38 | Interscalene | DA—to first rescue analgesic request with a VAS > 3. |
| [23]      | Madhusudhana 2011 | Upper limb surgery | 0.75% ropivacaine | 30 | Tramadol 50 mg | Landmark | 18–60 | 10 | Suprascavicular | DS—to recovery of sensation, DM, DA—no comments, OS—using pinprick test (complete block), OM—to motor block. |
| [24]      | Kaabachi 2009 | Hand surgery | 1.5% lidocaine (1/200,000) 40 ml | 30 | Tramadol 100 mg | Nerve stimulator | No details given (mean 33–39) | 34 | 35 | Axillary | DS—to recovery of sensory block using 3-point scale 0, DM—to recovery of motor block using 4-point scale 3, DA—to first rescue analgesic request, OS—to loss of sense to B-type pinprick test using 3-point scale 2 (anesthesia). |
| Reference | Studies | Surgery                     | Groups | LA volume for BPB | Groups (perineural adjuvant with LA) | Patient age, y | Patients (n) | Characteristics of block |
|-----------|---------|-----------------------------|--------|-------------------|--------------------------------------|----------------|--------------|-------------------------|
| [25]      | Dikmen 2009 | Arteriovenous fistula repair | 0.375% ropivacaine 38 ml | 40 | Tramadol 100 mg Control | 30–80 | 20 | Nerve stimulator Axillary Uremic patient, DS–to recovery of sensory block using 3-point scale 0, DM–to recovery of motor block using 3-point scale 0 (normal motor function), DA–to first rescue analgesic request, OS–using pinprick test (complete block), OM–to motor block using 3-point scale 2 (complete motor block). |
| [26]      | Kesimici 2007 | Hand and forearm surgery | 0.75% ropivacaine 40 ml+ | 42 | Tramadol 100 mg Control | 18–65 | 20 | Nerve stimulator Axillary Sensory and motor check for 4 nerves (radial, ulnar, median, musculocutaneous nerve), DS–to recovery of sensory block in all 4 nerves, DM–to recovery of motor block, DA–to first rescue analgesic request with VAS score > 4, OS–to loss of sense to B type pinprick using 3-point scale 2 in all 4 nerves, OM–to motor block using 3-point scale 2 (complete motor block) in all 4 nerves. |
| [27]      | Chattopadhyay 2007 | Upper limb surgery | 0.25% bupivacaine 38 ml + normal saline 2 ml | 40 | Tramadol 100 mg Control | 18–70 | 35 | Landmark Supraclavicular DS–to reappearance of pinprick response, DM–to modified Bromage scale 3, DA–to first rescue analgesic request, No clear definitions for OS, OM. |
| [28]      | Broch 2005 | Hand and forearm surgery | 1.5% prilocaine 40 ml | 40 | Tramadol 1.5 mg/kg Control | Above 18 | 20 | Landmark Axillary Sensory and motor check for 4 nerves (radial, ulnar, median, musculocutaneous nerve), DS–to recovery of sensory block in all 4 nerves, DM to recovery of motor block, DA–to first rescue analgesic request. |
| Reference | Studies | Surgery                | Groups                                                                 | LA volume for BPB | Patients (n) | Characteristics of block                          |
|-----------|---------|------------------------|------------------------------------------------------------------------|-------------------|--------------|--------------------------------------------------|
|           |         |                        | Groups (perineural adjuvant with LA)                                   |                   |              | Guidance | Type of BPB | Definition of sensory or motor block |
| [29]      | Robaux 2004 | Carpal tunnel release | 1.5% mepivacaine 40 ml                                               | 40                | 20           | Nerve stimulator | DS–to reappearance of pinprick using 3-point scale 2 (normal motor function), DM–to modified Bromage scale 3, OS–to light touch perception using 3-point scale 0 (no sensation). |
|           |         |                        | 40 Tramadol 40 mg                                                     |                   |              | Axillary  |                        |                                           |
|           |         |                        | Tramadol 100 mg                                                      |                   |              | Axillary  |                        |                                           |
|           |         |                        | Tramadol 200 mg                                                      |                   |              | Axillary  |                        |                                           |
|           |         |                        | Control                                                              |                   | 17           | Axillary  |                        |                                           |
|           |         |                        |                                                                      |                   |              |                      |                                           |
| [30]      | Antonucci 2001 | Carpal tunnel release | 0.75% ropivacaine 20 ml                                             | 20                | 23–63        | Nerve stimulator | DS–to recovery of sensory block, DA–full recovery of sense in hands, OS–to B type Pinprick test using 3-point scale 1 (analgesia). |
|           |         |                        | 20 Tramadol 100 mg                                                   |                   | 20           | Axillary  |                        |                                           |
|           |         |                        | Control                                                              |                   | 20           | Axillary  |                        |                                           |
|           |         |                        | Clonidine 1.5 g/kg                                                   |                   |              | Axillary  |                        |                                           |
|           |         |                        | Sufentanil 20 g                                                     |                   |              | Axillary  |                        |                                           |
| [31]      | Kapral 1999 | Forearm and hand surgery | 1% mepivacaine 40 ml                                               | 40                | 20           | Nerve stimulator | Sensory and motor check for 4 nerves (radial, ulnar, median, musculocutaneous nerve). DS–to offset of paresthesia, DM–to recovery of motor block. |
|           |         |                        | 40 Tramadol 100 mg                                                   |                   | 20           | Axillary  |                        |                                           |
|           |         |                        | Tramadol 100 mg (IV)                                                 |                   |              | Axillary  |                        |                                           |
|           |         |                        | Control                                                              |                   | 20           | Axillary  |                        |                                           |

DS, duration of sensory block; DM, duration of motor block; DA, duration of analgesia; OS, onset of sensory block; OM, onset of motor block; A type pinprick test using 3-point scale: 1 = no block (sharp sensation), 2 = partial block (blunt sensation, analgesia), 3 = complete block (no touch sensation, anesthesia). B type pinprick test using 3-point scale: 0 = normal sensation, 1 = loss of sensation of pinprick (analgesia), 2 = loss of sensation of touch (anesthesia). Modified Bromage scale using 4-point scale: 0 = no motion, 1 = finger movement, 2 = wrist flexion, 3 = elbow flexion. Motor block using 3-point scale: 0 = normal motor strength, 1 = reduced motor strength, 2 = complete motor block.

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Fig 2. Risk of bias summary for the included studies. Green circle, low risk of bias; yellow circle, unclear risk of bias; red circle, high risk of bias.

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time to onset of sensory block ($P_{\text{adj}} = 0.069381$). However, no publication bias was noted for the time to onset of motor block ($P_{\text{adj}} = 0.5354$). To compare $P$-values $< 0.1$ derived by Egger’s method, we performed a trim-and-fill analysis, and noticed a change in the significance of the results for the time to onset of sensory block (95% CI, -0.55 to 1.66). However, we noted no changes in the statistical significance of the results for duration of sensory block, motor block, and analgesia, indicating publication bias for these three parameters.

Results of the meta-analysis

1. Duration of sensory block [16–19, 21, 23–31]. The duration of sensory block was defined using the pinprick test [16–19, 21, 24, 25, 27, 29], recovery of sensation [23, 26, 28, 30], and offset of paresthesia [30] (Table 1). Adjuvant use of tramadol significantly prolonged the duration of sensory block by 61.5 min, with high heterogeneity (14 RCTs; 95% CI, -95.5 to -27.6; $I^2 = 97\%$; $P = 0.0004$) (Fig 3). In subgroup analysis of the BPB approach, the duration of sensory block was prolonged in the studies with axillary approach (MD, -45.6 min; $P = 0.0002$), but not in the studies with interscalene or supraclavicular approach (MD, -81.7 min; $P = 0.07$; Table 2) (S1 Table). In subgroup analysis of the tramadol dose, the duration of sensory block was prolonged in the studies with tramadol 100 mg (MD, -65.6 min; $P = 0.0006$), but not in the studies with tramadol 50 mg (MD, -35.8 min; $P = 0.48$; Fig 3). Sensitivity analysis did not detect any change in the overall significance of the duration of sensory block.

2. Duration of motor block [16–21, 23–29, 31]. The duration of motor block was defined using the modified Bromage scale [16–19, 27, 29], a 3-point scale [20, 21, 25], a 4-point scale [24], or recovery of motor block [26, 28, 31], as shown in Table 1. Use of tramadol as an

### Table 2. Subgroup meta-analysis by type of BPB approach.

|                  | Interscalene or supraclavicular approach | Auxillary approach | Subgroup differences | Test for overall effect $P$ |
|------------------|-----------------------------------------|--------------------|----------------------|---------------------------|
|                  | Studies (n) | MD (95% CI) | $I^2$ | $P$ | Studies (n) | MD (95% CI) | $I^2$ | $P$ | Studies (n) | MD (95% CI) | $I^2$ | $P$ |
| Duration of sensory block | 4 | -81.7 (-169.7, 6.3) | 96% | 0.07 | 10 | -45.6 (-69.9, -27.6) | 92% | 0.0002 | 0% | 0.44 | 0.0004 |
| Duration of motor block | 4 | -88.9 (-152.5, -25.4) | 86% | 0.006 | 10 | -54.9 (-92.1, -17.8) | 97% | 0.004 | 0% | 0.37 | 0.0003 |
| Duration of analgesia | 5 | -147.6 (-255.4, -39.8) | 94% | 0.007 | 9 | -107.7 (-165.0, -50.5) | 98% | 0.0002 | 0% | 0.52 | < 0.0001 |

A $P$ value $< 0.05$ was considered statistically significant. BPB, brachial plexus block; CI, confidence interval; $I^2$, statistic for heterogeneity; LA, local anesthesia; MD, mean difference (min). No studies using an infraclavicular approach were identified in the literature.
adjuvant prolonged the duration of motor block by 65.6 min, with high heterogeneity (14 RCTs; 95% CI, -101.5 to -29.7; $I^2 = 97%$; $P = 0.0003$; Fig 4). In subgroup analysis, the duration was prolonged in the studies with tramadol 100 mg (MD, -61.0 min; $P = 0.0002$), but not in the studies with tramadol 50 mg (MD, -72.0 min; $P = 0.27$; Fig 4) (S1 Table). Sensitivity analysis did not reveal any change in the overall significance of the duration of sensory block.

3. Duration of analgesia [16–28, 30].

The duration of analgesia was defined as the time to first request for rescue analgesia with a visual analog scale score $>3$ [22], or time to first request for rescue analgesia with a visual analog scale score $>4$ [26] (Table 1). Use of tramadol as an adjuvant significantly prolonged the duration of analgesia by 125.5 min with high heterogeneity (14 RCTs; 95% CI, -175.8 to -75.3; $I^2 = 98%$; $P < 0.0001$; Fig 5). In subgroup analysis, the duration was prolonged in the studies with tramadol 100 mg (MD, -120.7 min; $P < 0.00001$), but not in the studies with tramadol 50 mg (MD, -91.0 min; $P = 0.41$; Fig 5) (S1 Table). Sensitivity analysis did not reveal any change in the overall significance of the duration of analgesia.

4. Time to onset of sensory block [16–21, 23–27, 29, 30].

The time to onset of sensory block was defined using the pinprick test using a 3-point scale (A type [16]: 1 = no block [sharp sensation], 2 = partial block [blunt sensation, analgesia], 3 = complete block [no touch

Fig 4. Forest plot demonstrating the duration of motor block. Subgroup analysis according to dose of tramadol. CI, confidence interval; LA, local anesthesia; SD, standard deviation; Tra, tramadol.

Fig 5. Forest plot demonstrating the duration of analgesia. Subgroup analysis by dose of tramadol. CI, confidence interval; LA, local anesthesia; SD, standard deviation; Tra, tramadol.

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sensation, anesthesia]; B type [16, 20, 24, 26, 30]: 0 = normal sensation, 1 = loss of sensation of pinprick [analgesia], 2 = loss of sensation of touch [anesthesia], complete sensory block [21, 23], or light touch perception using a 3-point scale [29] (Table 1). Adjuvant use of tramadol shortened the time to onset of sensory block by 2.1 min, with high heterogeneity (13 RCTs; 95% CI, 1.1 to 3.1; $I^2 = 96%$; $P < 0.0001$; Fig 6A). Sensitivity analysis did not detect any change in the overall significance of the time to onset of sensory block.

5. Time to onset of motor block [16–21, 23, 25–27]. The time to onset of motor block was determined using the modified Bromage scale [16–19], a 3-point scale [20, 25, 26], or as 0 = no block, 1 = loss of passive movement of the lower extremities, 2 = inability to sit independently.

Table 3. Incidence of adverse effects of tramadol.

| Adverse effects | Number of tramadol/Total number of patients | RR (95% CI) | $P$ | NNT | Reference |
|-----------------|------------------------------------------|-------------|-----|-----|-----------|
| Nausea          | LA only: 225/453; LA with tramadol: 228/453 | 0.61 (0.29 to 1.30) | 0.61 | 22 | [16–18, 20–22, 25, 26, 29, 31] |
| Vomiting        | LA only: 230/463; LA with tramadol: 233/463 | 0.76 (0.30 to 1.93) | 0.34 | 39 | [17, 18, 20–22, 25–27, 29, 31] |
| Pruritus        | LA only: 115/233; LA with tramadol: 118/233 | 0.23 (0.04 to 2.00) | 0.18 | 30 | [17, 20, 21, 26, 29] |
| Sedation        | LA only: 89/121; LA with tramadol: 92/121 | 0.60 (0.16 to 2.29) | 0.42 | 32 | [16–18, 29] |

CI, confidence interval; LA, local anesthesia; NNT, number needed to treat; RR, risk ratio

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Table 4. Effect of tramadol as an adjuvant to local anesthesia according to tramadol dose (50 mg or 100 mg) for brachial plexus block.

| Outcomes                        | Illustrative comparative risks* (95% CI) | Participants (studies) | Quality of evidence (GRADE) | Comments | Test of overall effect (P) |
|---------------------------------|------------------------------------------|------------------------|----------------------------|----------|---------------------------|
| Duration of sensory block–tramadol 50 mg | Mean duration of sensory block–LA alone in the control group was 699.0 min | Mean duration of sensory block –LA with tramadol 50 mg in the intervention groups was 35.8 min longer (-134.26 longer) | 44 (2 studies) | low | P = 0.48 (not statistically significant) |
| Duration of sensory block–tramadol 100 mg | Mean duration of sensory block–LA alone in the control group was 239.3 min | Mean duration of sensory block –LA with tramadol 100 mg in the intervention groups was 65.6 min longer (28.37–102.92 longer) | 574 (12 studies) | moderate | P = 0.0006 |
| Duration of motor block–tramadol 50 mg | Mean duration of sensory block–LA alone in the control group was 657.0 min. | Mean duration of motor block–LA with tramadol 50 mg in the intervention groups was 72.0 min longer (-200.87 longer) | 44 (2 studies) | low | P = 0.27 (not statistically significant) |
| Duration of motor block–tramadol 100 mg | The mean duration of sensory block–LA alone in the control group was 256.8 min. | Mean duration of motor block–LA with tramadol 100 mg in the intervention groups was 61.0 min longer (28.62–93.37 longer) | 590 (12 studies) | moderate | P = 0.0002 |
| Duration of analgesia–tramadol 50 mg | Mean duration of sensory block–LA alone in the control group was 969 min. | Mean duration of analgesia–LA with tramadol 50 mg in the intervention groups was 91.0 min longer (-308.45 longer) | 44 (2 studies) | very low | P = 0.41 (not statistically significant) |
| Duration of analgesia–tramadol 100 mg | Mean duration of sensory block–LA alone in the control group was 351.9 min. | Mean duration of analgesia–LA with tramadol 100 mg in the intervention groups was 120.7 min longer (75.73–165.75 longer) | 633 (12 studies) | high | P < 0.00001 |
| Onset of sensory block–tramadol 50 mg | Mean duration of sensory block–LA alone in the control group was 7.2 min. | Mean onset of sensory block–LA with tramadol 50 mg in the intervention groups was 0.68 min shorter (-2.04 shorter) | 44 (2 studies) | low | P = 0.32 (not statistically significant) |
| Onset of sensory block–tramadol 100 mg | Mean duration of sensory block–LA alone in the control group was 16.2 min. | Mean onset of sensory block–LA with tramadol 100 mg in the intervention groups was 2.79 min shorter (0.81–4.76 shorter) | 550 (11 studies) | moderate | P = 0.006 |
| Onset of motor block–tramadol 50 mg | Mean duration of sensory block–LA alone in the control group was 10.9 min. | Mean onset of motor block–LA with tramadol 50 mg in the intervention groups was 0.75 min shorter (-2.65 shorter) | 44 (2 studies) | low | P = 0.44 (not statistically significant) |

(Continued)
complete motor block [21, 23] (Table 1). Adjuvant use of tramadol shortened the time to onset of motor block by 1.20 min with high heterogeneity (10 RCTs; 95% CI, 0.2 to 2.1; \( I^2 = 71\% \); \( P = 0.010 \); Fig 6B). Sensitivity analysis did not detect any change in the overall significance of the time of motor block.

### 6. Adverse effects.

Tramadol use did not change the incidence of adverse effects after BPB between the study groups: nausea (10 RCTs; RR, 0.61; 95% CI, 0.29 to 1.30; \( I^2 = 0\% \); \( P = 0.92 \); number needed to treat (NNT) = 22) [16–18, 20–22, 25, 26, 29, 31], vomiting (10 RCTs; RR, 0.76; 95% CI, 0.30 to 1.93; \( I^2 = 0\% \); \( P = 0.97 \); NNT = 39) [17, 18, 20–22, 25–27, 29, 31], pruritus (5 RCTs; RR, 0.23; 95% CI, 0.04 to 2.00; \( I^2 = 0\% \); \( P = 0.98 \); NNT = 30) [17, 20, 21, 26, 29], and sedation (4 RCTs; RR, 0.60; 95% CI, 0.16 to 2.29; \( I^2 = 0\% \); \( P = 0.93 \); NNT = 32) [16–18, 29] (Table 3).

### 7. GRADE guidelines.

In subgroup analysis according to tramadol dose, the duration of sensory block, motor block, and analgesia was prolonged in the studies with tramadol 100 mg for BPB but not in the studies with tramadol 50 mg. When the strength of the evidence was evaluated using the GRADE guidelines, there was high evidence that tramadol 100 mg with LA for BPB prolonged the duration of analgesia when compared with LA alone for BPB in patients undergoing upper extremity surgery (Table 4). The overall quality assessment was downgraded by inconsistency of effect, heterogeneity, and publication bias, but upgraded by the larger treatment effect and the presence of a dose-response relationship.

### Discussion

Our systemic review and meta-analysis indicates that use of tramadol as an adjuvant to LA in BPB prolongs the duration of sensory block, motor block, and analgesia and that it shortens the time to onset of sensory block and motor block without any change in adverse effects. There was some heterogeneity between the studies with regard to definitions of analgesia, sensory block, and motor block. There was high evidence according to GRADE guidelines that
Tramadol 100 mg with LA for BPB prolonged the duration of analgesia when compared with LA alone for BPB. To our knowledge, this is the first systematic review to evaluate the effect of tramadol as an adjuvant to LA in BPB for shoulder and upper extremity surgery.

In the past, there have been contradictory results regarding the effect of opioids as an adjuvant to LA in BPB. Saryazdi et al. [7] reported that addition of different opioids (meperidine, buprenorphine, morphine, and fentanyl) to lidocaine in axillary BPB achieved no statistically significant difference in duration of sensory block or motor block between the study groups.

Tramadol has unique modes of action, including weak opioid activity via the μ receptor, α2-adrenergic and serotonergic agonistic activity, and LA properties via blockade of K+ channels [33–35].

Our study included 16 studies that examined the effect of tramadol as an adjuvant to LA for BPB and also included quality control. However, the studies included in the review showed high heterogeneity. Generally, the type of surgery performed often determines the selection of BPB approach (interscalene, supraclavicular, infraclavicular, or axillary). This can affect the duration of analgesia at the surgical site. As an example, interscalene approaches are used for shoulder surgery, whereas axillary approaches tend to be used more for surgery on the forearm and hand. This difference in approach contributes to different results and clinical heterogeneity. We performed the meta-analysis using RevMan statistical software and performed subgroup analysis for various items (type of BPB approach, dose of tramadol, type of LA, volume of LA used for BPB) to identify the source of the heterogeneity (S1 Table). We could not find any difference in the duration of sensory, motor block, or analgesia according to type of BPB approach, but we did identify a dose-response effect of tramadol (50 mg, 100 mg) on the duration of sensory block, motor block, and analgesia.

Tramadol as an adjuvant for BPB in our review shortened the time to onset of sensory block and motor block. These findings are attributed to the potentiating effect of opioids and the peripheral LA-like effect of tramadol. The mechanism underlying the LA effect of tramadol is different from that of LA; the action of LA is generated by blocking Na+ channels, but tramadol exerts its effect by blocking K+ channels, as does meperidine [34]. A previous study showed that tramadol was as effective as lidocaine when injected subcutaneously in patients undergoing minor superficial procedures [36]. For the variable route of tramadol during BPB with LA, sensory and motor blocks enhanced by a perineural adjuvant to LA, but not by systemic administration (31).

Typical adverse effects of tramadol are headache, nausea, vomiting, dizziness, and sedation when it is used for analgesia (10, 31). We could not detect any differences in adverse effects between studies in our meta-analysis, which could reflect low plasma concentrations of tramadol. Use of tramadol as an adjuvant in BPB causes fewer symptoms than does intravenous administration of tramadol (36). There have been no reports of nerve damage attributed to tramadol in animal or human studies. The US Food and Drug Administration has not approved perineural administration of tramadol as it has for dexamethasone.

A recent systematic review of various adjuvants for peripheral nerve block [36] reported results for tramadol that contradict the findings of our systematic review. The authors of that review reported that perineural tramadol had no effect on sensory or motor block, and recommended not using tramadol as an adjuvant in peripheral nerve block. However, their review included only 5 RCTs of tramadol as an adjuvant to LA in BPB [22, 24, 26, 29, 31], and omitted many other relevant RCTs [16–20, 23, 25, 28]. Furthermore, they also included RCTs for other types of nerve block, such as psoas block [37] and paravertebral block [38]. Unlike that review of tramadol, we systematically searched for and identified the 16 studies on tramadol used as an adjuvant alone in BPB [16–31], and analyzed the effects of tramadol on sensory block, motor
block, and analgesia using systemic meta-analysis software. Generally, the degree of nerve block is determined by the type of nerve, the anatomic site of the nerve, and the type of nerve block.

Our review has several limitations. First, the studies included in the review contained considerably clinical heterogeneity with regard to type of BPB approach, dose and volume of drug, and type of guidance used for BPB. Based on the clinical assumption that different types of BPB may lead to different sensory or motor block characteristics and analgesia. Second, the definitions of outcomes of interest such as time to onset and duration of sensory block, motor block, and analgesia varied widely between the studies. Third, this review pertains to the duration of sensory block, motor block, and analgesia, and highlighted publication bias as ascertained by the trim-and-fill analysis. As a result, the findings of our meta-analysis were influenced by publication bias among the included studies.

However, our review also has several strengths. The main strength is that we tried to include all relevant databases and RCTs in our search. The methodology used was strong, with registration of the protocol for the review on PROSPERO and use of RevMan software.

Conclusions

Our study provides evidence that tramadol 100 mg is a potential adjuvant for use with LA in BPB. Adjuvant tramadol prolonged the duration of sensory block, motor block, and analgesia and shortened the time to onset of sensory block and motor block without altering the incidence of adverse effects.

Supporting information

S1 File. The search strategy.
(DOCX)

S1 Table. Summary of subgroup analysis from the results of meta-analysis.
(DOCX)

S2 Table. The PRISMA checklist.
(DOC)

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Tramadol and brachial plexus block

References

1. Choi S, Rodseth R, McCartney CJ. Effects of dexamethasone as a local anesthetic adjuvant for brachial plexus block: a systematic review and meta-analysis of randomized trials. British journal of anaesthesia. 2014; 112(3):427–39. Epub 2014/01/15. https://doi.org/10.1093/bja/aet417 PMID: 24413428.

2. Knezevic N, Antamombokul U, Candido K. Perioperative dexamethasone added to local anesthesia for brachial plexus block improves pain but delays block onset and motor blockade recovery. Pain Physician. 2015; 18:1–14. PMID: 25675053

3. Popping DM, Elias N, Marret E, Wenk M, Tramer MR. Clonidine as an adjuvant to local anesthetics for peripheral nerve and plexus blocks: a meta-analysis of randomized trials. Anesthesiology. 2009; 111(2):406–15. Epub 2009/07/16. https://doi.org/10.1097/ALN.0b013e3181aa897 PMID: 19602964.

4. Abdallah FW, Brull R. Facilitatory effects of perineural dexamethomidine on neuraxial and peripheral nerve block: a systematic review and meta-analysis. British journal of anaesthesia. 2013; 110(6):915–25. Epub 2013/04/17. https://doi.org/10.1093/bja/aet066 PMID: 23587874.

5. Park CH. Comparison of morphine and tramadol in thoracolumbar epidural injections for lumbar radicular pain. The Korean journal of pain. 2013; 26(3):265–9. Epub 2013/07/19. https://doi.org/10.3344/kjp.2013.26.3.265 PMID: 23862000; PubMed Central PMCID: PMCPMC3710940.

6. Mukherjee K, Das A, Basunia SR, Dutta S, Mandal P, Mukherjee A. Evaluation of Magnesium as an adjuvant in Ropivacaine-induced supraventricular brachial plexus block: A prospective, double-blinded randomized controlled study. Journal of research in pharmacy practice. 2014; 3(4):123–9. Epub 2014/04/26. https://doi.org/10.4103/2279-042X.145387 PMID: 25535620; PubMed Central PMCID: PMCPMC462858.

7. Saryazdi H, Yazdani A, Sajedi P, Aghadavoudi O. Comparative evaluation of adding different opiates (morphine, meperidine, buprenorphine, or fentanyl) to lidocaine in duration and quality of axillary brachial plexus block. Advanced biomedical research. 2015; 4:232. Epub 2015/12/09. https://doi.org/10.4103/2277-9175.167901 PMID: 26645017; PubMed Central PMCID: PMCPMC4647124.

8. Gormley WP, Murray JM, Fee JP, Bower S. Effect of the addition of alfentanil to lignocaine during axillary brachial plexus anaesthesia. British journal of anaesthesia. 1996; 76(6):802–5. Epub 1996/06/01. PMID: 8679353.

9. Fanelli G, Casati A, Magistris L, Berti M, Albertin A, Scarioni M, et al. Fentanyl does not improve the nerve block characteristics of axillary brachial plexus anaesthesia performed with ropivacaine. Acta anaesthesiologica Scandinavica. 2001; 45(5):590–4. Epub 2001/04/20. PMID: 11309009.

10. Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. Drugs. 2000; 60(1):139–76. Epub 2001/04/10. PMID: 10929933.

11. Grond S, Sablotzki A. Clinical pharmacology of tramadol. Clinical pharmacokinetics. 2004; 43(13):879–923. Epub 2004/10/29. PMID: 15509185.

12. Kayser V, Besson JM, Guilbaud G. Evidence for a noradrenergic component in the antinociceptive effect of the analgesic agent tramadol in an animal model of clinical pain, the arthritic rat. Eur J Pharmacol. 1992; 224(1):83–8. Epub 1992/11/24. PMID: 1360407.

13. Arcioni R, della Rocca M, Romano S, Romano R, Pietropaoli P, Gasparetto A. Ondansetron inhibits the analgesic effects of tramadol: a possible 5-HT(3) spinal receptor involvement in acute pain in humans. Anesthesia and analgesia. 2002; 94(6):1553–7, table of contents. Epub 2002/05/29. PMID: 12032025.

14. Mert T, Gunes Y, Guven M, Gunay I, Gocmen C. Differential effects of lidocaine and tramadol on modified nerve impulse by 4-aminopyridine in rats. Pharmacology. 2003; 69(2):68–73. Epub 2003/08/21. PMID: 12928579.

15. Altunkaya H, Ozar Y, Kargi E, Babuccu O. Comparison of local anesthetic effects of tramadol with lidocaine for minor surgical procedures. British journal of anaesthesia. 2003; 90(3):320–2. Epub 2003/02/21. PMID: 12594144.

16. Nagpal V, Rana S, Singh J, Chaudhary S. Comparative study of systemically and perineurally administered tramadol as an adjunct for supraclaviculare brachial plexus block. Journal of anaesthesiology, clinical pharmacology [Internet]. 2015; 31(2):[191–5 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/490/CN-01088490/frame.html.

17. Khosa AH, Asad N, Durrani H. Does the addition of Tramadol to local anaesthetic mixture improve the quality of axillary brachial plexus block: A comparative study at the teaching hospital, Dera Ghazi Khan. Pakistan Journal of Medical and Health Sciences. 2015; 9(4):1120–3.

18. Senel AC, Ukcio O, Timurkaynak A. Does the addition of tramadol and ketamine to ropivacaine prolong the axillary brachial plexus block? BioMed Research International. 2014; 2014.

19. Trabelsi W, Lebbi A, Romdhani C, Naas I, Sammoud W, Elaskri H, et al. Dexamethasone provides longer analgesia than tramadol when added to lidocaine after ultrasound guided supraclaviculare brachial plexus block. A randomized, controlled, double blinded study. Analg Resusc: Curr Res 2013; 2:2.
20. Yurtlu BS, Hanci V, Ege A, Bostankolu SE, Ayoğu H, Özoçek Turan I. Tramadol as an adjunct for levobupivacaine in axillary plexus blockade: A prospective, randomized, double-blind study. Turkish Journal of Medical Sciences. 2012; 42(1):55–62.

21. Geze S, Ulusoy H, Ertürk E, Cekic B, Arduc C. Comparison of local anesthetic mixtures with tramadol or fentanyl for axillary plexus block in orthopaedic upper extremity surgery. European Journal of General Medicine. 2012; 9(2):118–23.

22. Alemanno F, Ghisi D, Fanelli A, Faliva A, Pergolotti B, Bizzarri F, et al. Tramadol and 0.5% levobupivacaine for single-shot interscalene block: effects on postoperative analgesia in patients undergoing shoulder arthroplasty. Minerva anesthesiologica. 2012; 78(3):291–6. Epub 2011/10/06. PMID: 21971437.

23. Madhusudhana R, Kumar K, Kumar R, Potli S, Karthik D, Kapil M. Supravclavicular brachial plexus block with 0.75% ropivacaine and with additives tramadol, fentanyl—a comparative pilot study. Int J Biol Med Res. 2011; 2:1061–3.

24. Kaabachi O, Ouezni R, Koubaa W, Ghrab B, Zargouni A, Ben Abdelaziz A. Tramadol as an adjuvant to lidocaine for axillary brachial plexus block. Anesthesia and analgesia. 2009; 108(1):367–70. Epub 2008/12/20. https://doi.org/10.1213/ane.0b013e3181f0c68 PMID: 19095875.

25. Dikmen B GM, Horasanli E, Örnek D, Pekel M, Selçuk A. The effects of adding tramadol to ropivacaine on axillary brachial plexus blockade in uremic patients. Turk J Med Sci 2009; 39:733–9.

26. Kesimci E, Izdes S, Gözdemir M, Kanbak O. Tramadol does not prolong the effect of ropivacaine 7.5 mg/ml for axillary brachial plexus block. Acta anaesthesiologica Scandinavica. 2007; 51(6):736–41. Epub 2007/04/12. https://doi.org/10.1111/j.1399-6576.2007.01308.x PMID: 17425616.

27. Chattopadhyay S, Mitra LG, Biswas BN, Majumder P. Tramadol as an adjuvant for brachial plexus block. Journal of Anaesthesiology Clinical Pharmacology. 2007; 23(2):187–90.

28. Robaux S, Blunt C, Viel E, Cuvillon P, Nougquier P, Dautel G, et al. Tramadol added to 1.5% mepivacaine for axillary brachial plexus block improves postoperative analgesia dose-dependently. Anesth Analg. 2004; 98(4):1172–7, table of contents. Epub 2004/03/26. PMID: 15041620.

29. Antonucci S. Comparison between clonidine, sufentanil and tramadol. Minerva Anestesiol 2001; 67:23–7. PMID: 11279374.

30. Capral S, Gollmann G, Walli B, Likar R, Sladen RN, Weinstabl C, et al. Tramadol added to mepivacaine prolongs the duration of an axillary brachial plexus blockade. Anesthesia and analgesia. 1999; 88(4):853–6. Epub 1999/04/09. PMID: 10195537.

31. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed). 2011; 343:d5928. Epub 2011/10/20. https://doi.org/10.1136/bmj.d5928 PMID: 22008217; PubMed Central PMCID: PMCPMC3196245.

32. Sousa AM, Ashmawi HA, Costa LS, Posso IP, Slullitel A. Percutaneous sciatic nerve block with tramadol induces analgesia and motor blockade in two animal pain models. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas. 2012; 45(2):147–52. Epub 2011/12/21. https://doi.org/10.1590/S0100-879X2011007500164 PMID: 22183244; PubMed Central PMCID: PMCPMC3854253.

33. Yalcin I, Aksu F. Involvement of potassium channels and nitric oxide in tramadol antinociception. Pharmacology, biochemistry, and behavior. 2005; 80(1):69–75. Epub 2005/01/18. https://doi.org/10.1016/j.pbb.2004.10.020 PMID: 15652382.

34. Budd K, Langford R. Tramadol revisited. British journal of anaesthesia. 1999; 82(4):493–5. Epub 1999/09/03. PMID: 10472210.

35. Kirksey MA, Haskins SC, Cheng J, Liu SS. Local Anesthetic Peripheral Nerve Block Adjuvants for Prolongation of Analgesia: A Systematic Qualitative Review. PloS one. 2015; 10(9):e0137312. Epub 2015/09/12. https://doi.org/10.1371/journal.pone.0137312 PMID: 26355598; PubMed Central PMCID: PMCPMC4655865.

36. Mannion S, O’Callaghan S, Murphy DB, Shorten GD. Tramadol as adjunct to psoas compartment block with levobupivacaine 0.5%. a randomized double-blinded study. British journal of anaesthesia. 2005; 94 (3):352–6. Epub 2004/12/21. https://doi.org/10.1093/bja/aei057 PMID: 15608044.

37. Omar A, Mansour M, Abdelwahab H, Aboushanab O. Role of ketamine and tramadol as adjuncts to bupivacaine 0.5% in paravertebral block for breast surgery: A randomized double-blind study. Egypt J Anaesth. 2011; 27:101–5.