Systematic Review

Efficacy of Nalbuphine as a Local Anesthetic Adjuvant for Brachial Plexus Block: A Systematic Review and Meta-analysis

Jingyao Jiang, MM[1,2], Xu Cheng, MM[1], Donghang Zhang, MD[1,2], and Cheng Zhou, PhD[2]

From: [1]Department of Anesthesiology, West China Hospital of Sichuan University, Chengdu, China; [2]Laboratory of Anesthesia and Critical Care Medicine, National-Local Joint Engineering Research Centre of Translational Medicine of Anesthesiology, West China Hospital of Sichuan University, Chengdu, China

Address Correspondence:
Donghang Zhang, MD
Department of Anesthesiology
West China Hospital of Sichuan University
Chengdu, 610041, China
E-mail: zhangdhscu@163.com

Disclaimer: Jingyao Jiang and Xu Cheng contributed equally to this work. There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 07-17-2022
Revised manuscript received: 08-12-2022
Accepted for publication: 10-10-2022

Free full manuscript: www.painphysicianjournal.com

Background: Nalbuphine has been increasingly used as a local anesthetic adjuvant to extend the duration of analgesia in brachial plexus block (BPB).

Objectives: To systematically and firstly evaluate the available evidence on the efficacy of nalbuphine as an adjuvant to local anesthetics in BPB.

Study Design: Systematic review and meta-analysis.

Methods: Cochrane Central Register of Controlled Clinical Trials, Cochrane Database of Systematic Reviews, Medline, Embase, Scopus, Web of Science, EBSCO, PubMed, and additional databases were searched. Randomized controlled trials comparing combination of perineural nalbuphine with local anesthetics to local anesthetics alone in BPB for upper extremity surgical procedures were eligible for inclusion.

Results: Nineteen randomized controlled trials involving 1,355 patients met the inclusion criteria. Perineural use of nalbuphine prolonged the duration of analgesia in BPB (mean difference [MD], 162.5; 95% confidence interval [CI], 119.0 to 205.9; $P < 0.00001$; very low quality of evidence). The duration of sensory block was also extended (MD, 141.6; 95% CI, 100.3 to 182.9; $P < 0.00001$; very low quality of evidence). Furthermore, nalbuphine shortened the onset time of sensory block (MD, -2.6; 95% CI, -3.6 to -1.5; $P < 0.00001$; very low quality of evidence). There were no significant differences in side effect-related outcomes, including nausea (risk radio [RR], 1.56; 95% CI, 0.82 to 2.59; $P = 0.17$; moderate quality of evidence) and vomiting (RR, 1.41; 95% CI, 0.66 to 3.02; $P = 0.38$; moderate quality of evidence).

Limitations: The study was limited by substantial heterogeneity, a relatively small sample size and difference-in-differences in how outcomes of interest were described and assessed.

Conclusions: Perineural use of nalbuphine in BPB is an effective strategy for analgesia in adult patients undergoing upper extremity surgery.

Key words: Nalbuphine, brachial plexus block, local anesthetics, nerve block, local anesthetic adjuvant, analgesia, meta-analysis, systematic review

Pain Physician 2022: 25:E1339-E1349

Peripheral nerve blocks using local anesthetics are most commonly used in limb surgeries for analgesia. Nevertheless, single-shot peripheral nerve blocks have a primary drawback: their limited duration of action, which especially isn't enough for postoperative analgesia (1-4). Increasing evidences revealed that the addition of perineural adjuvants, such as dexamethasone, dexmedetomidine, or clonidine, to local anesthesia facilitates the extension of the benefits of analgesia beyond the duration of anesthesia (1,3,4).

Nalbuphine, a mixed k-agonist-μ-antagonist opioid (1,2,4), has been increasingly used as a local anesthetic adjuvant to extend the duration of analgesia in various regional anesthetic techniques (5-7). However,

results regarding analgesic effects of peripheral nalbuphine varied in randomized controlled trials (RCTs). Therefore, it is worthwhile to perform a systematic review and meta-analysis to evaluate the efficacy of nalbuphine as an adjuvant to local anesthetics in brachial plexus block (BPB).

Methods

We registered protocol for this meta-analysis at the International Platform of Registered Systematic Reviews and Meta-analysis Protocols (registration number INPLASY202230064) and were carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (8).

Literature Search

Two authors (J.J. and X.C.) independently searched electronic data-bases, including the Cochrane Central Register of Controlled Clinical Trials, Cochrane Database of Systematic Reviews, Medline, Embase, Scopus, Web of Science, EBSCO, and PubMed from their inception to March 31, 2022. We searched for the following population terms: (1) nalbuphine, and (2) brachial plexus block or nerve block. The search terms included all combination of Emtree terms, medical subject headings, and free text. Furthermore, the authors (J.J. and X.C.) searched Google Scholar (Google, Mountain View, CA,) for any potentially relevant studies that were not founded after retrieving the primary database described above.

Eligibility Criteria

Eligible studies were included according to the following population, intervention, control, and outcomes criteria: (1) design: RCTs; (2) population: patients undergoing upper extremity surgical procedures, including elbow, forearm, and hand under BPB; (3) intervention and control: combined nalbuphine and local anesthesia vs local anesthesia alone; (4) outcomes: primary outcome of interest was the duration of analgesia, and secondary outcomes were duration of sensory and motor block, its onset times and side effects, including nausea, vomiting, bradycardia, hypotension, sedation, and pruritus. Studies that did not report at least one of the above outcomes were excluded.

Study Selection

Study identification was independently conducted by 2 authors (J.J. and X.C.). We retrieved full-text articles of potentially relevant articles after an initial screening of screening titles and abstracts. Consensus on the inclusion of qualifying studies was reached between the 2 authors (J.J. and X.C.). Other authors (D.Z. and C.Z.) helped resolve disagreements.

Outcome Definition

Duration of analgesia (minutes) was defined as the time taken from sensory block onset to the first analgesic request. Duration of sensory and motor block were defined as the time interval from the end of local anesthetics injection to fully restored sensory and motor abilities, respectively. Onset time of sensory and motor block were defined as a period of time after the local anesthetics injections are complete until full sensory and motor block occurs, respectively.

Data Extraction

Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA) was used to create a standardized form for data collection. When the discrepancies in the data extraction occurs, 2 authors (J.J. and X.C.) turn to assistance of another author (D.Z. and C.Z.). The extracted information included surgical and anesthetics settings, age, weight, concentration and bulk of local anesthetics, perineural dose of nalbuphine, and the localization technique. If 2 intervention/control groups with different doses were compared in one study, data were pooled into a single group by following the methods described in the Cochrane Handbook for Systematic Reviews (9).

Assessment of Risk of Bias

We used the Cochrane Collaboration Risk of Bias Tool, which was embedded in Review Manager (RevMan; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to assess the risk of bias (10). This tool contains the following domains: random sequence generation, allocation concealment, blinding of patients and personnel (performance bias), blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases.

Assessment of Quality of Evidence

Evidence was graded according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE), which used sequentially assessing evidence quality, evaluating the risk-benefit balance, and then assessing the effectiveness of the recommendations (11). According to GRADE, synthesized evidence is categorized into 4 categories based on ele-

ments, including study quality, consistency, directness, precision, as well as publication bias: (1) high quality: the estimates of effect are likely to remain accurate with further research; (2) moderate quality: additional research could significantly alter the estimation of this effect; (3) low quality: there is a high probability that further research will have a significant effect on confidence in the estimation effect and possibly result in a change to the estimate; and (4) very low quality: we are unsure of the estimate.

Heterogeneity, Subgroup Analysis, Meta-Regression, and Sensitivity Analyses

Heterogeneity was quantificationally described using the I^2 statistic and was thought as "substantial" when $I^2 > 75\%$. Analyses of subgroups based on these items were performed to explore the effects of heterogeneity: (1) doses of perineural nalbuphine (10 mg and/or 20 mg), (2) type of local anesthetics used (long-lasting vs moderate-lasting local anesthetics), and (3) the localization technique (nerve stimulation and ultrasound [US]). We performed meta-regression if ≥ 10 trials were included within the covariate group. Additionally, sensitivity analysis was carried out if limited number of trials were included (≤ 9).

Statistical Analysis

Statistical analysis was conducted using Review Manager Version 5.3 (RevMan; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Continuums and dichotomies were analyzed using a random-effects model. Forest plots were described to exhibit and evaluate treatment effects. The mean difference (MD) and 95% confidence interval (CI) were evaluated for continuous outcomes, and risk radio (RR) with 95% CI for dichotomous outcomes. For the evaluation of treatment effects, forest plots were constructed (Stata version 14.1; StataCorp, College Station, TX). Statistical significance was defined as $P < 0.05$.

Results

Study Selection

Our search strategy initially identified 1,762 citations (Cochrane Register of Controlled Trials 10, Cochrane Database of Systematic Reviews 0, Medline 624, Embase 173, Scopus 189, Web of Science 66, EBSCO 53, PubMed 37, and additional records 610).

After elimination of duplicates, a total of 417 records remained. After screening of titles and abstracts, 377 records were excluded. Forty full-text articles were retained and assessed for their eligibility. Ultimately, 19 RCTs recruiting 1,355 surgical patients met the inclusion criteria. The flow diagram of study selection was shown in Fig. 1.

Characteristics of Included Studies

All included RCTs performed single-shot nerve blocks at the level of the brachial plexus, of which 18 trials at the supraclavicular level and one trial at the interscalene level (12). Seventeen studies compared the combination of local anesthetics with nalbuphine to local anesthetics alone, but 2 also included another dose of local anesthetics (13) and nalbuphine (14). The techniques of nerve block localization were performed under US in 16 studies (12-27), nerve stimulation in 2 studies (28,29), and a combination of nerve stimulation and US in one study (30). The vast majority of doses of nalbuphine were 10 mg, except for 2 studies (13,16) that used doses of 20 mg and one study (14) that used doses of both 10 mg and 20 mg. The characteristics of included studies were summarized in Table 1.

Risk of Bias Assessment

In most studies, selection bias, attrition bias, and reporting bias were low. One study (15) reported no details about the randomization method and was assessed as having a high risk of bias. Moreover, the majority of studies were advised to have an unclear risk of selection and performance bias due to a lack of sufficient details of blinding and concealment of sequence allocation. The reviewers' consensus assessment of the risk is shown in Fig. 2.

Results of Meta-analyses

Duration of Analgesia

Eighteen studies (12-16,18-30) reported the effects of nalbuphine on the duration of analgesia. The pooled results showed that adding perineural nalbuphine in the BPB prolonged the duration of analgesia (MD, 162.5; 95% CI, 119.0 to 205.9; $P < 0.00001$; $I^2 = 100\%$; very low quality of evidence). Based on the dose of nalbuphine, subgroup analysis was performed, and the results indicated that both 10 mg (MD, 168.4; 95% CI, 120.7 to 216.1; $P < 0.00001$; $I^2 = 100\%$) and 20 mg (MD, 120.1; 95% CI, 63.0 to 177.1; $P < 0.0002$; $I^2 = 88\%$) nalbuphine in BPB prolonged the duration of analgesia as compared to the control (Fig. 3 and Table 2).

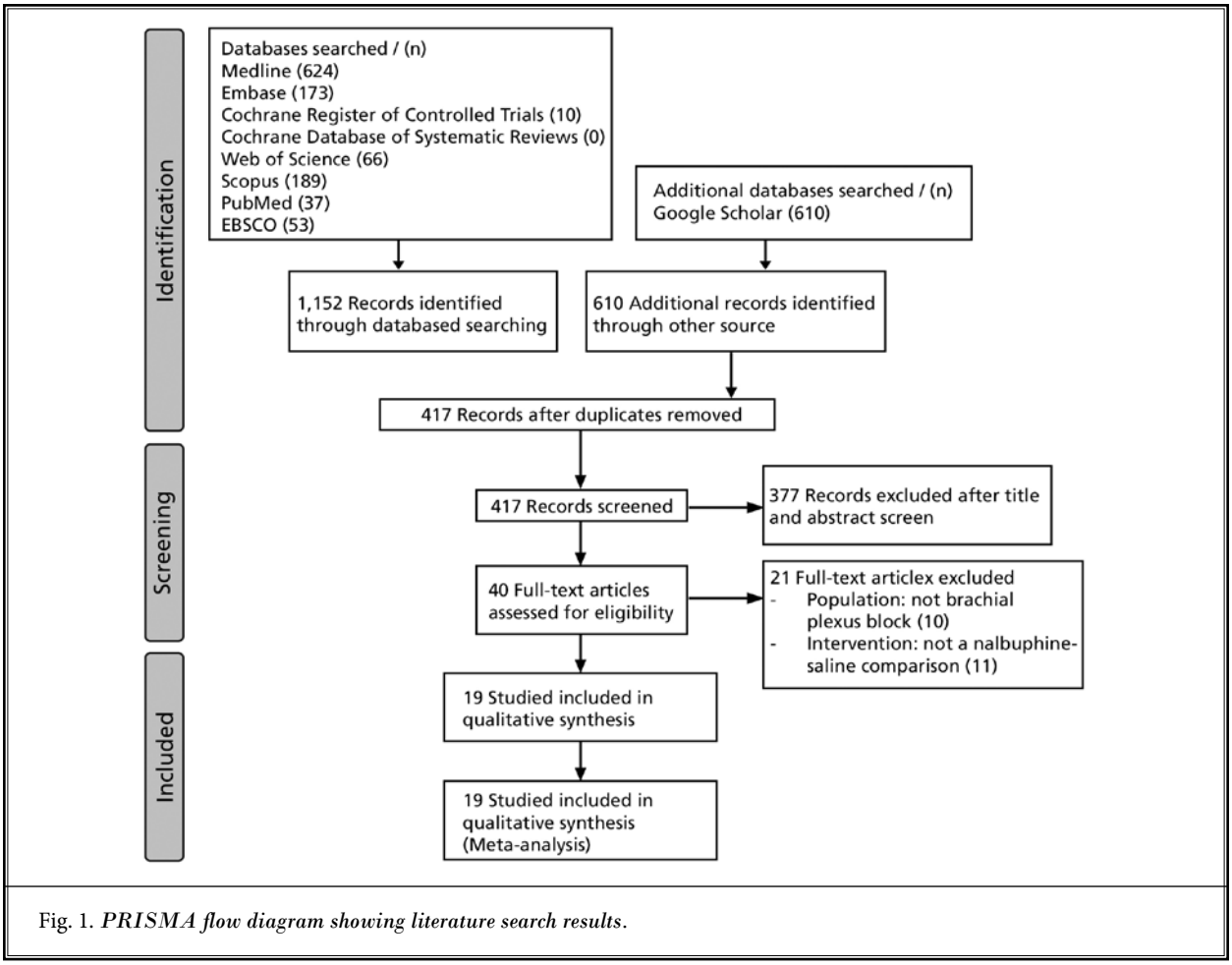

Fig. 1. *PRISMA flow diagram showing literature search results.*

Duration of Sensory Block

Seventeen studies (13-18,20-30) reported the effects of nalbuphine on the duration of sensory block. The pooled results showed that adding perineural nalbuphine in the BPB prolonged the duration of sensory block (MD, 141.6; 95% CI, 100.3 to 182.9; $P < 0.00001$; $I^2 = 100\%$; very low quality of evidence). Based on the dose of nalbuphine, subgroup analysis was performed, and the results indicated that both 10 mg (MD, 144.6; 95% CI, 98.2 to 191.0; $P < 0.00001$; $I^2 = 100\%$) and 20 mg (MD, 126.5; 95% CI, 71.0 to 182.0; $P < 0.00001$; $I^2 = 93\%$) perineural nalbuphine in BPB significantly prolonged the duration of sensory block as compared to the control (Fig. 4a and Table 2).

Onset Time of Sensory Block

All included studies (12-30) reported the effects of nalbuphine on the onset time of sensory block. The pooled results showed that adding perineural nalbuphine in the BPB accelerated the onset time of sensory block (MD, -2.6; 95% CI, -3.6 to -1.5; $P < 0.00001$; $I^2 = 97\%$; very low quality of evidence). Based on the dose of nalbuphine, subgroup analysis was performed, and the results indicated that both 10 mg (MD, -2.9; 95% CI, -4.2 to -1.7; $P < 0.00001$; $I^2 = 97\%$) and 20 mg (MD, -0.8; 95% CI, -1.6 to 0.1; $P = 0.03$; $I^2 = 70\%$) perineural nalbuphine accelerated the onset time of sensory block for BPB as compared to the control (Fig. 4b and Table 2).

Duration of Motor Block

All included studies (12-30) reported the effects of nalbuphine on the duration of motor block. The pooled results showed that perineural nalbuphine in the BPB prolonged the duration of motor block (MD, 95.2; 95% CI, 49.5 to 141.0; $P < .00001$; $I^2 = 100\%$; very low quality

Table 1. *Trial characteristics*.

Study	Type of Surgery	Age (y) Nalbuphine/ NS	Weight (kg) Nalbuphine/ NS	n	Groups (n)	Local Anaesthetics	Technique
Abaidullah et al 2021 (15)	Upper Limb	36 (12)/ 37 (11)	N/D	96	Nalbuphine 1 mL (10 mg) (48), NS (48)	Ropivacaine 0.75%, 25 mL	US
Abdelhamid et al 2018 (13)	Hand, Forearm	34 (11)/ 33 (11)	72 (12)/ 74 (13)	135	Nalbuphine 1 mL (20 mg) (45), NS (45)	Levobupivacaine 0.25%/ 0.5%, 25 mL	US
Abdelhaq et al 2016 (16)	Hand, Forearm	44 (6)/ 48 (5)	70 (1)/ 68(1)	56	Nalbuphine 1 mL (20 mg) (28), NS (28)	Bupivacaine 0.5%, 25 mL	US
Aggarwal et al 2021 (30)	Upper Limb	36 (13)/ 38 (14)	63 (8)/ 63 (7)	60	Nalbuphine 1 mL (10 mg) (30), NS (30)	Levobupivacaine 0.5%, 29 mL	US; Nerve Stimulation
Arish et al 2021 (17)	Hand, Forearm	35(11)/ 33 (9)	67 (12)/ 66 (12)	69	Nalbuphine 1 mL (10 mg) (35), NS (34)	Ropivacaine 0.5%, 24 mL	US
Das et al 2017 (29)	Hand, Forearm	37 (9)/41 (10)	55 (8)/52 (8)	78	Nalbuphine 2 mL (10 mg) (39), NS (39)	Levobupivacaine 0.5%, 30 mL	Nerve Stimulation
Farrukh et al 2020 (18)	Upper Limb	37 (10)/ 38 (9)	N/D	60	Nalbuphine 10 mg (30), NS (30)	Ropivacaine 0.75%, 25 mL	US
Gupta et al 2016 (19)	Hand, Forearm	33 (17)/ 34 (14)	64 (8)/ 58 (10)	60	Nalbuphine 1 mL (10 mg) (30), NS (30)	Bupivacaine 0.5%, 20 mL	US
Imran-Ul-Hassan et al 2020 (20)	Upper Limb	36 (12)/ 37 (11)	N/D	48	Nalbuphine 1 mL (10 mg) (24), NS (24)	Ropivacaine 0.75%, 25 mL	US
Jadeja et al 2019 (28)	Upper Limb	33 (13)/ 37 (14)	57 (5)/ 56 (4)	60	Nalbuphine 1 mL (10 mg) (30), NS (30)	Ropivacaine 0.5%, 30 mL	Nerve Stimulation
Jain et al 2019 (21)	Upper Limb	36 (14)/ 36 (14)	55 (5)/ 56 (7)	100	Nalbuphine 1 mL (10 mg) (50), NS (50)	Ropivacaine 0.5%, 20 mL	US
Kalika et al 2020 (14)	Upper Limb	47 (11)/ 44 (10)	70 (10)/ 69 (8)	90	Nalbuphine 2 mL (10 mg) (30), Nalbuphine 2 mL (20 mg) (30), NS (30)	Ropivacaine 100 mg, 18 mL	US
Khamis et al 2021 (22)	Upper Limb	37 (12)/ 39 (13)	37 (12)/ 39 (13)	90	Nalbuphine 2 mL (10 mg) (30), Verapamil (30)*, NS (30)	Bupivacaine 0.5%, 30 mL	US
Madhusudhanan et al 2021 (23)	Hand, Forearm	34 (17)/ 35 (14)	64 (8)/ 58 (10)	60	Nalbuphine 1 mL (10 mg) (30), NS (30)	Bupivacaine 0.5%, 20 mL	US
Mehta et al 2022 (24)	Upper Limb	42 (9)/ 40 (10)	65 (9)/ 64 (8)	60	Nalbuphine 1 mL (10 mg) (30), NS (30)	Bupivacaine 0.5%, 20 mL	US
Mohamed et al 2021 (25)	Mid Humerus, Elbow, Forearm, or Hand	38 (9)/ 38 (9)	74 (6)/ 75 (6)	90	Nalbuphine 1 mL (10 mg) (30), Dexmedetomidine (30)*, NS (30)	Bupivacaine 0.5%, 24 mL	US
Nazir et al 2017 (26)	Upper Limb	31 (14)/ 33 (12)	55 (8)/ 53 (11)	60	Nalbuphine 1 mL (10 mg) (30), NS (30)	Bupivacaine 0.375%, 30 mL	US
Yadav et al 2019 (27)	Mid-Humerus, Elbow, Forearm, or Hand	29 (12)/ 32 (9)	52 (11)/ 56 (10)	60	Nalbuphine 1 mL (10 mg) (30), NS (30)	Ropivacaine 0.75%, 29 mL	US
Annamalai et al 2018 (12)	Shoulder and Arm	41 (9)/ 40 (10)	69 (10)/ 68 (8)	60	Nalbuphine 1 mL (10 mg) (29), NS (28)	Bupivacaine 0.75%, 20 mL	US

Abbreviations: y, year; US, ultrasound; kg, kilogram; mL, milliliter; mg, milligram; N/D, not defined; NS, normal saline; n, number. (*) excluded from the analysis.

of evidence). Based on the dose of nalbuphine, subgroup analysis was performed, and the results indicated that both 10 mg (MD, 106.3; 95% CI, 56.4 to 156.2; $P < 0.00001$; $I^2 = 100\%$) and 20 mg (MD, 31.7; 95% CI, -25.9 to 89.4; $P < 0.00001$; $I^2 = 95\%$) perineural nalbuphine significantly prolonged the duration of motor block for BPB as compared to the control (Supplementary Fig. 1a and Table 2).

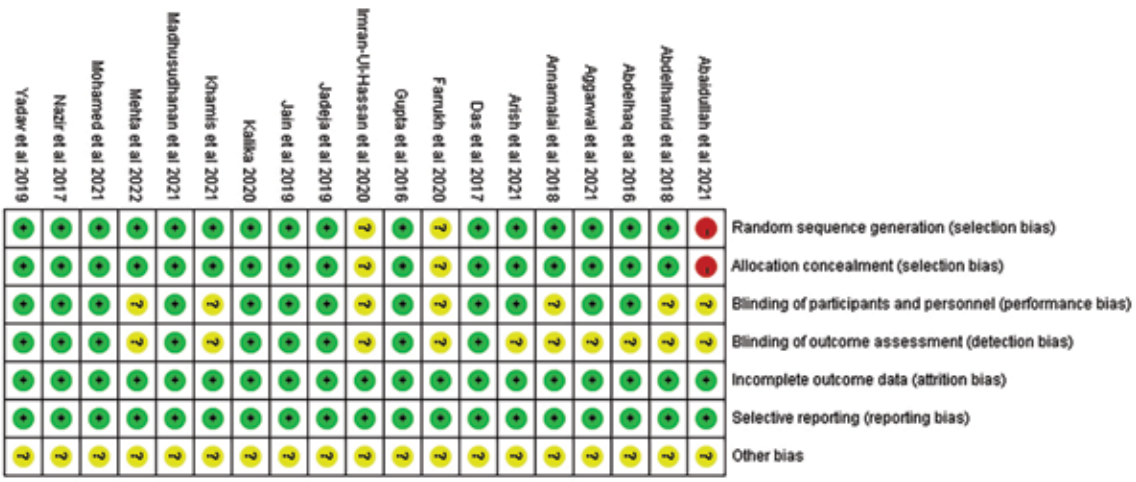

Fig. 2. *Summary of bias assessment using the Cochrane risk of bias tool.*

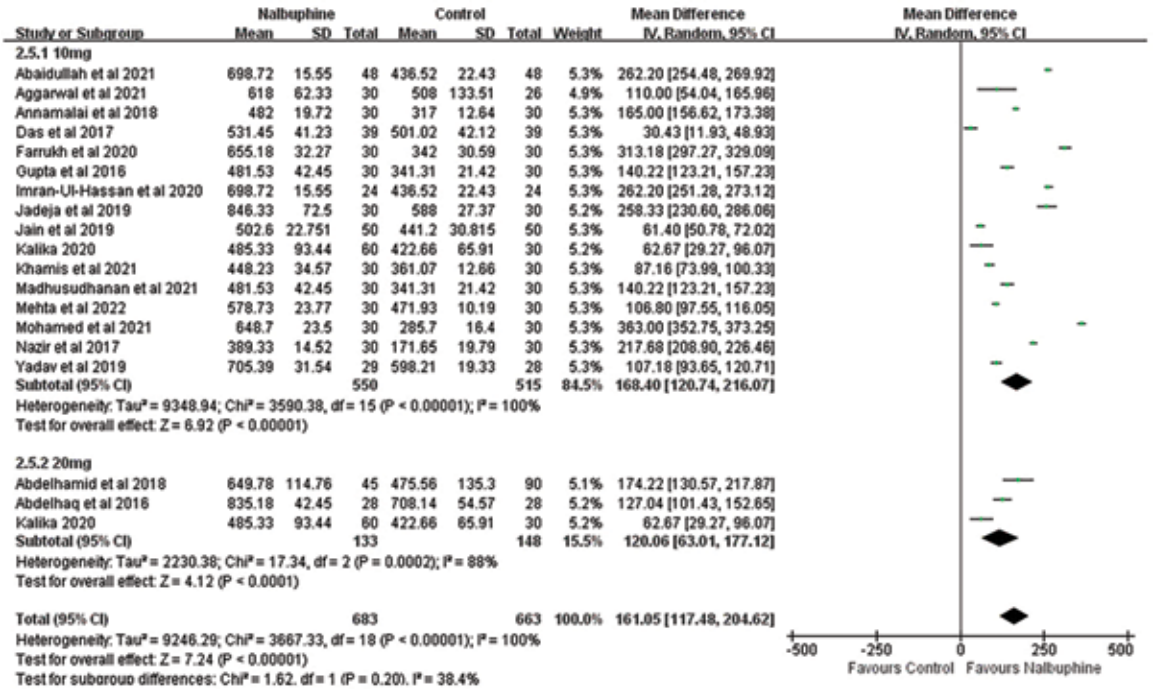

Fig. 3. *Forest plot depicting the effect of perineural nalbuphine on the duration of analgesia. The pooled estimates of the mean difference are shown. 95% CIs are shown as lines for individual studies and as rhombus for pooled estimates.*

Onset Time of Motor Block

All included studies (12-30) reported the effects of nalbuphine on the onset time of motor block. The pooled results showed that adding perineural nalbuphine in BPB accelerated the duration of analgesia (MD, -3.1; 95% CI, -4.2 to -2.0; $P < 0.00001$; $I^2 = 97\%$;

Table 2. *Summary of findings, summary of results and GRADE of evidence.*

Outcome	Number of Studies Included	Group		MD/RR (95% CI)	*P* value for Overall Effect	I^2 Test for Heterogenelty	*P* value for Heterogenelty	Quality of Evidence (GRADE)
		Nalbuphine /n	Control /n					
Duration of Analgesia	18	623	633	162.5 (119.0 to 205.9)	< 0.00001	100%	< 0.00001	⊕OOO VERY LOW
Duration of Sensory Block	17	598	608	141.6 (100.3 to 182.9)	< 0.00001	100%	< 0.00001	⊕OOO VERY LOW
Duration of Motor Block	19	658	667	95.2 (49.5 to 141.0)	< 0.0001	100%	< 0.00001	⊕OOO VERY LOW
Onset Time of Sensory Block	19	658	667	-2.56 (-3.63 to -1.49)	< 0.00001	97%	< 0.00001	⊕OOO VERY LOW
Onset Time of Motor Block	19	658	697	-3.1 (-4.2 to -2.0)	< 0.00001	97%	< 0.00001	⊕OOO VERY LOW
Analgesic Consumption		99	95	-32.0 (-37.9 to -26.1)	< 0.00001	63%	0.07	⊕OOO VERY LOW
Nausea	9	25/344	14/359	1.56 (0.82 to 2.59)	0.17	0%	0.42	⊕⊕⊕O MODERATE
Vomiting	9	16/344	10/359	1.41 (0.66 to 3.02)	0.38	0%	0.66	⊕⊕⊕O MODERATE
Bradycar-dia	11	2/384	0/348	4.35 (0.22 to 86.8)	0.34	N/A	N/A	⊕OOO VERY LOW
Hypotension	11	1/384	0/348	2.61 (0.11 to 61.5)	0.55	N/A	N/A	⊕⊕⊕O MODERATE
Sedation	3	10/114	4/155	2.39 (0.78 to 7.3)	0.13	0%	0.66	⊕OOO VERY LOW
Pruritus	7	9/264	10/257	1.06 (0.06 to 17.2)	0.97	80%	0.008	⊕OOO VERY LOW

Abbreviations: n, number; MD, mean difference; RR, risk ration; CI, confidence interval; N/A, not applicable; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

very low quality of evidence). Based on the dose of nalbuphine, subgroup analysis was performed, and the results indicated that both 10 mg (MD, -3.5; 95% CI, -4.7 to -2.3; $P < 0.00001$; $I^2 = 97\%$) and 20 mg (MD, -1.0; 95% CI, -1.9 to -0.2; $P = 0.05$; $I^2 = 65\%$) perineural nalbuphine accelerated the onset time of motor block for BPB as compared to the control (Supplementary Fig. 1b and Table 2).

Analgesics Consumption

Three studies (25,29,30) reported the effects of nalbuphine on the analgesics consumption. Compared with the control, the addition of perineural nalbuphine (10 mg) in the BPB reduced the consumption of analgesics during postoperative 24 hours (MD, -32.0; 95% CI, -37.9 to -26.1; $P < 0.00001$; $I^2 = 63\%$; very low quality of evidence) (Table 2).

Side Effect-Related Outcomes

Nausea was reported in 9 studies (13,14,18,19,21,23-25,29), vomiting in 9 studies (13,14,18,19,21,23-25,29), bradycardia in 11 studies (12,14,17,19,21,23-25,27,28,30), hypotension in 11 studies (12,14,17,19,21,23-25,27,28,30), sedation in 3 studies (13,29,30), and pruritus in 7 studies (13,14,19,23,24,29,30). No significant difference was found in the risk of nausea (RR 1.56; 95% CI, 0.82 to 2.59; $P = 0.17$; $I^2 = 0\%$; moderate quality of evidence), vomiting (RR 1.41; 95% CI, 0.66 to 3.02; $P = 0.38$; $I^2 = 0\%$; moderate quality of evidence), bradycardia (RR 4.35; 95% CI, 0.22 to 86.8; $P = 0.34$; I^2 = not applicable [N/A]; very low quality of evidence), hypotension (RR 2.61; 95% CI, 0.11 to 61.5; $P = 0.55$; I^2 = N/A; moderate quality of evidence), sedation (RR 2.39; 95% CI, 0.78 to 7.3; $P = 0.13$; $I^2 = 0\%$; very low quality of evidence), and pruritus (RR 1.06; 95% CI, 0.06 to 17.2; $P = 0.97$; $I^2 = 80\%$; very low quality of evidence) (Table 2).

An overview of pooled results for all outcomes were summarized in Table 2.

Meta-Regression

Subgroup analysis and meta-regression of pairwise

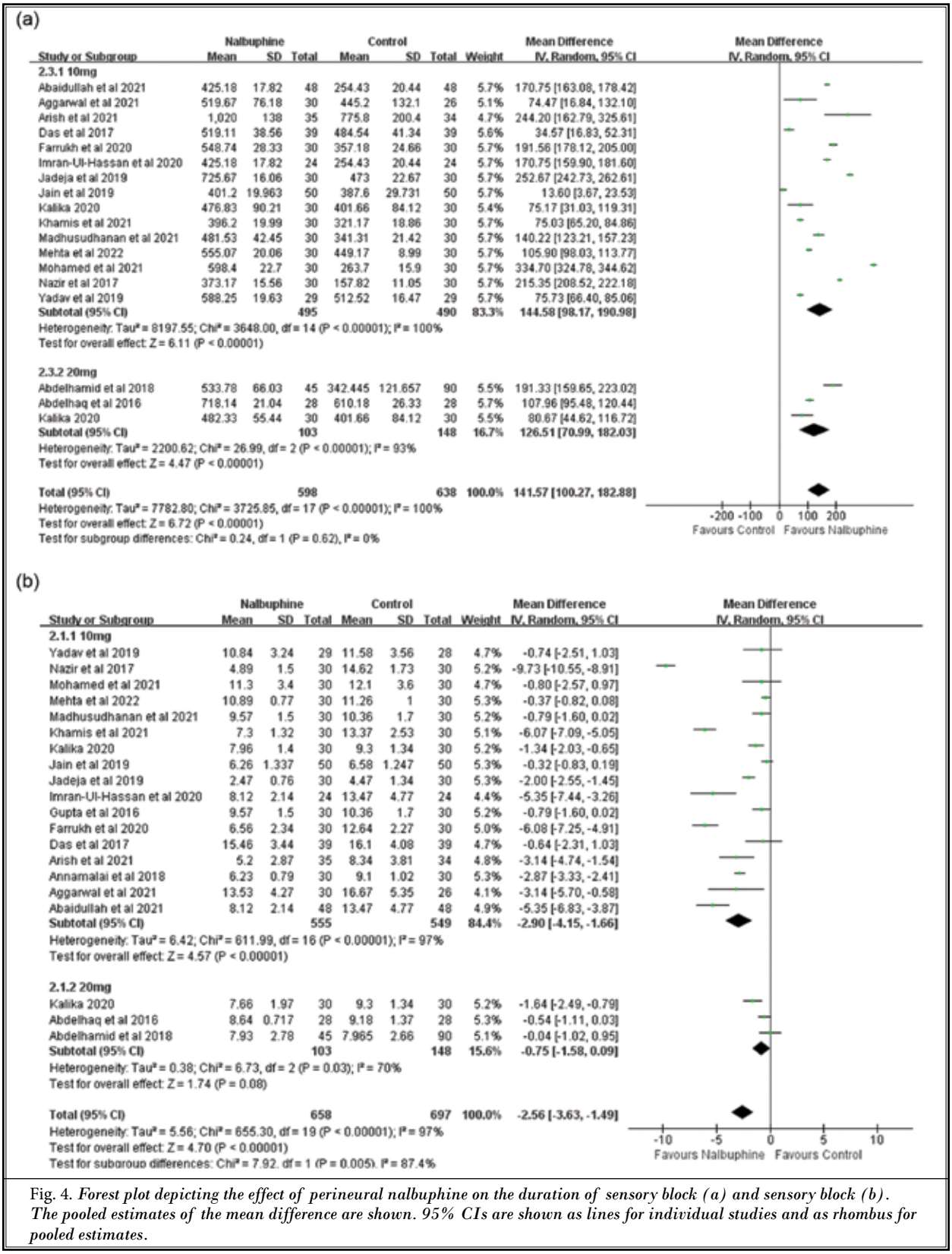

Fig. 4. *Forest plot depicting the effect of perineural nalbuphine on the duration of sensory block (a) and sensory block (b). The pooled estimates of the mean difference are shown. 95% CIs are shown as lines for individual studies and as rhombus for pooled estimates.*

comparisons based on predefined covariates (mentioned in the Methods section) revealed that the duration of analgesia was independent of the block guidance technique, local anesthetics type, and nalbuphine dose (Supplementary Fig. 2).

Discussion

It is the first meta-analysis to evaluate the efficacy of perineural nalbuphine as an adjuvant to local anesthetics in BPB. Based on 19 RCTs, the present meta-analysis demonstrated that BPB adjuvant with perineural nalbuphine achieves significant analgesic benefits, including a prolonged period of analgesia and reduced cumulative analgesic use for the 24 hours following surgery. Perineural nalbuphine also extended the duration of sensory and motor block as well as accelerated its onset time. Furthermore, perineural nalbuphine did not increase the incidence of side effects, such as nausea and vomiting.

The most commonly used doses of nalbuphine for BPB were 10 mg and 20 mg (13,19). Kalika et al (14) studied the effects of 10 mg vs 20 mg nalbuphine as an adjuvant to ropivacaine for supraclavicular BPB during upper arm surgery. According to their findings, there was no significant difference between both groups in terms of analgesic and block benefits (14). Consistent with this, our subgroup analysis results demonstrated that 10 mg and 20 mg nalbuphine groups did not differ statistically. Some large sample and well-designed RCTs are needed to confirm the dose-related effects of nalbuphine as an adjuvant in BPB.

Our results supported that perineural nalbuphine exhibits a facilitatory effect in BPB. However, in half of the included studies, no statistically significant difference was reported between the nalbuphine group and the control group regarding the onset time of both motor and sensory blocks. The small sample sizes and differences in the measurement techniques might explain for this discrepancy.

In the present meta-analysis, the combined results showed that perineural use of nalbuphine in BPB did not increase the prevalence of side effects, including the pruritus, which is commonly seen after opioids (31). Moreover, Ibrahim et al (32) reported that intrathecal bupivacaine with morphine adjuvant with nalbuphine significantly decreased the incidence of postoperative pruritus. And Jannuzzi (33) recommended that nalbuphine could be used as a treatment of opioid-induced pruritus. Therefore, perineural nalbuphine was considered as a safe strategy for BPB.

The analgesic mechanism of perineural nalbuphine is still unclear. Firstly, opioids may exert analgesic effects through peripheral opioid receptors (7). Furthermore, by blocking sodium channels incorporated into the nerve membranes, nalbuphine can promote local anesthetic action (34). Finally, systemic absorption of perineural nalbuphine may contribute to analgesia (31).

Different adjuvants have been added to local anesthetics to improve the safety and duration of analgesia in peripheral nerve blocks (1-3), of which dexmedetomidine is commonly used (35). Jiang et al (36) compared dexmedetomidine with nalbuphine as adjuvant for BPB. Their studies found that nalbuphine when compared with dexmedetomidine prolonged block and analgesia duration, hastened its onset time, and decreased analgesic consumption for 24 hours following surgery. Mohamed et al (25) compared the effects of dexmedetomidine with nalbuphine as a adjuvant on BPB. Their results suggested that sensory and motor block analgesia did not differ significantly between dexmedetomidine and nalbuphine groups; however, dexmedetomidine resulted in significantly prolongation of sedation when combined with bupivacaine for supraclavicular BPB. These studies suggested that nalbuphine was as effective as dexmedetomidine for BPB as a perineural adjuvant. In future studies, it is interesting to compare the analgesic effects of nalbuphine with another commonly used adjuvant, dexamethasone, in the BPB.

Limitations

This meta-analysis has several limitations. First, substantial heterogeneity existed due to several contributors, such as a variety of surgical and anesthetic settings, usage of local anesthetics, and localization technology. Second, most included studies had a relatively small sample size, which may increase the likelihood of publication bias and type I error. Third, there were some differences in how outcomes of interest were described and assessed, which could account for the observed heterogeneity.

Conclusions

In summary, our results demonstrated that perineural use of nalbuphine as an adjuvant to local anesthetics in BPB is an effective strategy for analgesia in adult patients undergoing upper extremity surgery.

References

1. Prasad GVK, Khanna S, Jaishree SV. Review of adjuvants to local anesthetics in peripheral nerve blocks: Current and future trends. *Saudi J Anaesth* 2020; 14:77-84.
2. Patacsil JA, McAuliffe MS, Feyh LS, Sigmon LL. Local anesthetic adjuvants providing the longest duration of analgesia for single-injection peripheral nerve blocks in orthopedic surgery: A literature review. *AANA Journal* 2016; 84:95-103.
3. Desai N, Kirkham KR, Albrecht E. Local anaesthetic adjuncts for peripheral regional anaesthesia: A narrative review. *Anaesthesia* 2021; 76(suppl 1):100-109.
4. Opperer M, Gerner P, Memtsoudis SG. Additives to local anesthetics for peripheral nerve blocks or local anesthesia: A review of the literature. *Pain Management* 2015; 5:117-128.
5. Gress K, Charipova K, Jung JW, et al. A comprehensive review of partial opioid agonists for the treatment of chronic pain. *Best Practice & Research Clinical Anaesthesiology* 2020; 34:449-461.
6. Pallasch TJ, Gill CJ. Butorphanol and nalbuphine: A pharmacologic comparison. *Oral Surgery, Oral Medicine, and Oral Pathology* 1985; 59:15-20.
7. Stein C. Opioid receptors on peripheral sensory neurons. *Advances in Experimental Medicine and Biology* 2003; 521:69-76.
8. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ (Clinical Research ed)* 2021; 372:n71.
9. Higgins JPT, Deeks J. Selecting studies and collecting data. In: Higgins JPT, Thomas J (eds). *Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series*. John Wiley & Sons, Inc., Hoboken, NJ, 2008.
10. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clinical Research ed)* 2011; 343:d5928.
11. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* 2011; 64:401-406.
12. Annamalai AMR, Chandran P. A critical evaluation of an effect of nalbuphine as an adjuvant to bupivacaine for ultrasound guided interscalene brachial plexus block. *Indian Journal of Anesthesia and Analgesia* 2018; 5:993-997.
13. Abdelhamid BM, Omar H. Nalbuphine as an adjuvant to 0.25% levobupivacaine in ultrasound-guided supraclavicular block provided prolonged sensory block and similar motor block durations (RCT). *Journal of Anesthesia* 2018; 32:551-557.
14. Kalika P, Xue R, Zheng J, et al. Efficacy of nalbuphine as an adjuvant to ropivacaine in ultrasound guided supraclavicular brachial block – a prospective randomized controlled study. *Clinical Journal of Pain* 2020; 36:267-272.
15. Abaidullah K, Khan AA, Tariq N, Sadiq I. Effectiveness of nalbuphine with ropivacaine in supraclavicular brachial plexus block in patients undergoing upper limb surgeries. *Pakistan Journal of Medical and Health Sciences* 2021; 15:1791-1793.
16. Abdelhaq MM, Elramely MA. Effect of nalbuphine as adjuvant to bupivacaine for ultrasound-guided supraclavicular brachial plexus block. *Open Journal of Anesthesiology* 2016; 6:20.
17. Arish B, Hariharasudhan B, Ranjan R, et al. Anaesthetic efficacy of nalbuphine as an adjuvant to ropivacaine in ultrasound guided supraclavicular brachial plexus blockade: A randomised controlled trial. *Journal of Clinical & Diagnostic Research* 2021; 15:1-4.
18. Farrukh R, Rana AR, Ahmed. Compare the analgesic efficacy of nalbuphine with ropivacaine versus ropivacaine alone in supraclavicular brachial plexus block. *Pakistan Journal of Medical & Health Sciences* 2020; 14:1187-1189.
19. Gupta K, Jain M, Gupta PK, Rastogi B, Zuberi A, Pandey MN. Nalbuphine as an adjuvant to 0.5% bupivacaine for ultrasound-guided supraclavicular brachial plexus blockade. *Indian Journal of Pain* 2016; 30:176.
20. Imran-Ul-Hassan S, Qureshi SA, Qurban F. Determine the effectiveness of nulbuphine with ropivacaine in supraclavicular brachial plexus block. *Pakistan Journal of Medical and Health Sciences* 2020; 14:1572-1574.
21. Jain K, Sethi SK, Gupta S, Khare A. Efficacy of nalbuphine as an adjuvant to 0.5% ropivacaine for ultrasound-guided supraclavicular brachial plexus block in upper limb surgeries: A prospective randomized double-blind study. *The Indian Anaesthetists Forum* 2019; 20:82.
22. Khamis MI, Mohamed AS, El Azazy HM, El Ozairy HS, Mohamed MM. A comparative study between the effect of verapamil versus nalbuphine as an adjuvant in supraclavicular brachial plexus block. *Ain-Shams Journal of Anesthesiology* 2021; 13:1-6.
23. Madhusudhanan R. *Effect of Nalbuphine as Adjuvant to 0.5% Bupivacaine in Ultrasound Guided Supraclavicular Brachial Plexus Block*. Thanjavur Medical College, Thanjavur, 2021.
24. Mehta SS, Patel NS, Patel KA, Panchani PP. Nalbuphine as an adjuvant to bupivacaine for supraclavicular brachial plexus block under ultrasonography guidance. *Journal of Evolution of Medical and Dental Sciences* 2022; 11:72-77.
25. Mohamed HS, Gad GS. Bupivacaine-Dexmedetomidine versus bupivacaine-nalbuphine in ultrasound-guided supraclavicular brachial plexus block: A prospective, randomized, double-blind study. *Ain Shams Journal of Anesthesiology* 2021; 13:2.
26. Nazir N, Jain S. Randomized controlled trial for evaluating the analgesic effect of nalbuphine as an adjuvant to bupivacaine in supraclavicular block under ultrasound guidance. *Anesthesia, Essays and Researches* 2017; 11:326.
27. Yadav VK, Choudhary AK, Prasad MK, Jheetay GS, Kumar A, Shahid R. Role of nalbuphine as an adjuvant to ropivacaine in supraclavicular block – a randomized control study. *Anaesthesia, Pain and Intensive Care* 2019; 23:186-191.
28. Jadeja P, Gohel JA. Comparative evaluation of ropivacaine alone with ropivacaine nalbuphine combination in supraclavicular brachial plexus block for upper limb surgery. *International Journal of Scientific Study* 2019; 7:85-91.
29. Das A, RoyBasunia S, Mukherjee A, et al. Perineural nalbuphine in ambulatory upper limb surgery: A comparison of effects of levobupivacaine with and without nalbuphine as adjuvant in supraclavicular brachial plexus block–a prospective, double-blinded, randomized controlled study. *Anesthesia, Essays and Researches* 2017; 11:40.
30. Aggarwal S, Kumari A, Gupta R. Twenty-Four-Hour requirement of rescue analgesia after upper limb surgery under supraclavicular brachial plexus block: A role of nalbuphine as an adjuvant to levobupivacaine. *AMEI's Curr Trends Diagn Treat* 2021; 5:16-20.
31. Sehgal N, Smith HS, Manchikanti L. Peripherally acting opioids and clinical

implications for pain control. *Pain Physician* 2011; 14:249-258.

32. Ibrahim AS, Aly MG, Thabet ME, Abdelaziz MR. Effect of adding nalbuphine to intrathecal bupivacaine with morphine on postoperative nausea and vomiting and pruritus after elective cesarean delivery: A randomized double blinded study. *Minerva Anestesiologica* 2019; 85:255-262.
33. Jannuzzi RG. Nalbuphine for treatment of opioid-induced pruritus: A systematic review of literature. *The Clinical Journal of Pain* 2016; 32:87-93.
34. Likar R, Koppert W, Blatnig H, et al. Efficacy of peripheral morphine analgesia in inflamed, non-inflamed and perineural tissue of dental surgery patients. *J Pain Symptom Manage* 2001; 21:330-337.
35. Vorobeichik L, Brull R, Abdallah FW. Evidence basis for using perineural dexmedetomidine to enhance the quality of brachial plexus nerve blocks: A systematic review and meta-analysis of randomized controlled trials. *British Journal of Anaesthesia* 2017; 118:167-181.
36. Jiang C, Xie W, Xie H, Xie W, Kang Z, Liu N. Nalbuphine exhibited a better adjuvant than dexmedetomidine in supraclavicular brachial plexus block in youths. *Clinical Neuropharmacology* 2020; 43:134-138.