Systematic Review

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

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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 (Rev-Man; 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 elements, 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 l² statistic and was thought as "substantial" when l² > 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 (longlasting vs moderate-lasting local anesthetics), and (3) the localization technique (nerve stimulation and ultrasound [US]). We performed meta-regression if \geq 10 trials were included within the covariate group. Additionally, sensitivity analysis was carried out if limited number of trials were included (\leq 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 (Cl) were evaluated for continuous outcomes, and risk radio (RR) with 95% Cl 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).



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% Cl, 49.5 to 141.0; P < .00001; $l^2 = 100\%$; very low quality

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

Table 1. Trial characteristics.

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; I² = 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).



	Naf	buphine		¢	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	N, Random, 95% Cl
2.5.1 10mg									
Abaidullah et al 2021	698.72	15.55	48	436.52	22.43	48	5.3%	262.20 [254.48, 269.92]	
Aggarwal et al 2021	618	62.33	30	508	133.51	26	4.9%	110.00 [54.04, 165.96]	
Annamalai et al 2018	482	19.72	30	317	12.64	30	5.3%	165.00 [156.62, 173.38]	-
Das et al 2017	531.45	41.23	39	501.02	42.12	39	5.3%	30.43 [11.93, 48.93]	-
Farrukh et al 2020	655.18	32.27	30	342	30.59	30	5.3%	313.18 [297.27, 329.09]	-
Gupta et al 2016	481.53	42.45	30	341.31	21.42	30	5.3%	140.22 [123.21, 157.23]	-
Imran-UI-Hassan et al 2020	698.72	15.55	24	436.52	22.43	24	5.3%	262.20 [251.28, 273.12]	-
Jadeja et al 2019	846.33	72.5	30	588	27.37	30	5.2%	258.33 [230.60, 286.06]	-
Jain et al 2019	502.6	22.751	50	441.2	30.815	50	5.3%	61.40 [50.78, 72.02]	-
Kalika 2020	485.33	93.44	60	422.66	65.91	30	5.2%	62.67 [29.27, 96.07]	-
Khamis et al 2021	448.23	34.57	30	361.07	12.66	30	5.3%	87.16 [73.99, 100.33]	-
Madhusudhanan et al 2021	481.53	42.45	30	341.31	21.42	30	5.3%	140.22 [123.21, 157.23]	-
Mehta et al 2022	578.73	23.77	30	471.93	10.19	30	5.3%	106.80 [97.55, 116.05]	-
Mohamed et al 2021	648.7	23.5	30	285.7	16.4	30	5.3%	363.00 [352.75, 373.25]	-
Nazir et al 2017	389.33	14.52	30	171.65	19,79	30	5.3%	217.68 [208.90, 226.46]	-
Yadav et al 2019	705.39	31.54	29	598.21	19.33	28	5.3%	107.18 [93.65, 120.71]	-
Subtotal (95% CI)			550			515	84.5%	168.40 [120.74, 216.07]	•
Heterogeneity: Tau ² = 9348.94	I: Chi ² = 3	590.38, 6	f= 15 ((P < 0.00)	001); P=	100%			
Test for overall effect: Z = 6.92	(P < 0.00	001)		,					
2.5.2 20mg									
Abdelhamid et al 2018	649.78	114.76	45	475.58	135.3	90	5.1%	174.22 [130.57, 217.87]	
Abdelhag et al 2016	835.18	42.45	28	708.14	54.57	28	5.2%	127.04 [101.43, 152.65]	-
Kalika 2020	485.33	93.44	60	422.66	65.91	30	5.2%	62.67 [29.27, 96.07]	-
Subtotal (95% CI)			133			148	15.5%	120.06 [63.01, 177.12]	•
Heterogeneity: Tau ^a = 2230.38 Test for overall effect: Z = 4.12	; Chi ^a = 17 (P < 0.00	7.34, df= 01)	2 (P =	0.0002);	l² = 88%				
Total (95% CI)			683			663	100.0%	161.05 [117.48, 204.62]	◆
Heterogeneity: Tau* = 9246.29	; Chi# = 3	667.33, ¢	f= 18 /	(P < 0.00f	001); I ^p =	100%			tan 200 0 200 000
Test for overall effect Z = 7.24	(P < 0.00	001)							-500 -250 0 250 500
Test for subaroup differences:	: Chi#=1.f	62. df = 1	(P = 0)	20), I ^a = 3	38.4%				Favours Control Favours Mateuphine

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; $I^2 = 97\%$;

	Number	mber Group		мр/рр	P value	12 Л. с		Quality of	
Outcome	of Studies Included	Nalbuphine /n	Control /n	(95% CI)	for Overall Effect	1- Test for Heterogenelty	P value for Heterogenelty	Evidence (GRADE)	
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 Consumpution		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	

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

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% Cl, -4.7 to -2.3; P < 0.00001; $I^2 = 97\%$) and 20 mg (MD, -1.0; 95% Cl, -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 studies (12,14,17,19,21,23-25,27,28,30), seda-11 tion 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 guality of evidence), vomiting (RR 1.41; 95% CI, 0.66 to 3.02; P = 0.38; I² = 0%; moderate quality of evidence), bradycardia (RR 4.35; 95% CI, 0.22 to 86.8; P = 0.34; I² = not applicable [N/A]; very low quality of evidence), hypotension (RR 2.61; 95% CI, 0.11 to 61.5; P = 0.55; I² = 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; I² = 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

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(a)									
(4)	Nal	buphine		c	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
2.3.1 10mg									
Abaidullah et al 2021	425.18	17.82	48	254.43	20.44	48	5.7%	170.75 [163.08, 178.42]	
Arish et al 2021	1.020	138	30	775.8	200.4	20	4.7%	244.20 [162.79. 325.61]	
Das et al 2017	519.11	38.56	39	484.54	41.34	39	5.6%	34.57 [16.83, 52.31]	-
Farrukh et al 2020	548.74	28.33	30	357.18	24.66	30	5.7%	191.56 [178.12, 205.00]	-
Imran-UI-Hassan et al 2020	425.18	17.82	24	254.43	20.44	24	5.7%	170.75 [159.90, 181.60]	-
Jadeja et al 2019	725.67	16.06	30	473	22.67	30	5.7%	252.67 [242.73, 262.61]	
Kalika 2020	401.2	90.21	30	401.66	29.731	30	5.4%	76 17 [31 03 119 31]	
Khamis et al 2021	396.2	19.99	30	321.17	18.86	30	5.7%	75.03 [65.20, 84.86]	-
Madhusudhanan et al 2021	481.53	42.45	30	341.31	21.42	30	5.7%	140.22 [123.21, 157.23]	-
Mehta et al 2022	555.07	20.06	30	449.17	8.99	30	5.7%	105.90 [98.03, 113.77]	•
Mohamed et al 2021	598.4	22.7	30	263.7	15.9	30	5.7%	334.70 [324.78, 344.62]	
Vadav et al 2017	599.25	19.50	30	157.82	16.47	20	5.7%	215.35 [208.52, 222.18] 75 72 [66.40, 95.06]	
Subtotal (95% CI)	000.20	10.00	495	012.02	10.47	490	83.3%	144.58 [98.17, 190.98]	•
Heterogeneity: Tau ^a = 8197.5	5; Chi# = 36	548.00, d	f= 14 (P	< 0.0000)1); I ^e = 10	0%			
Test for overall effect: Z = 6.11	I (P < 0.000	001)							
2 2 2 20mg									
Abdelhamid et al 2019	533 78	66.03	45	342 445	121 657	90	5.5%	101 33 [150 65 223 02]	
Abdelhag et al 2016	718.14	21.04	28	610.18	26.33	28	5.7%	107.96 195.48, 120.441	-
Kalika 2020	482.33	55.44	30	401.66	84.12	30	5.5%	80.67 [44.62, 116.72]	
Subtotal (95% CI)			103			148	16.7%	126.51 [70.99, 182.03]	•
Heterogeneity: Tau ^a = 2200.6	2; Chi ^a = 26	5.99, df =	2 (P < 0	.00001);	P= 93%				
Test for overall effect Z = 4.47	r (P < 0.000)01)							
Total (95% CI)			598			638	100.0%	141.57 [100.27, 182.88]	•
Heterogeneity: Tau ^a = 7782.8	0; Chi ^a = 37	25.85, d	f = 17 (P	< 0.0000)1); I ^e = 10	0%			
Test for overall effect: Z = 6.72	2 (P < 0.000	001)							-200 -100 0 100 200 Favours Control Favours Nalbuphine
Test for subgroup differences	:: Chi ² = 0.2	24, df = 1	(P = 0.6	2), I [#] = 09	6				
(b)									
\ <i>/</i>									
	,	Malhumh	ino		`ontrol			Mean Difference	Mean Difference
Study or Subgroup	l Mea	Nalbuph in S	ine D Tota	(I Mean	Control SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV. Random, 95% Cl
Study or Subgroup 2.1.1 10mg	Mea	Nalbuph in S	ine D Tota	(Mean	Control SD	Total	Weight	Mean Difference IV, Random, 95% Cl	Mean Difference IV. Random, 95% Cl
Study or Subgroup 2.1.1 10mg Yadav et al 2019	Mea 10.8	Nalbuph <u>m S</u> 34 3.2	ine <u>D Tota</u> 4 29	(<u>Mean</u> 3 11.58	SD 3.56	Total 28	Weight 4.7%	Mean Difference N. Random, 95% Cl -0.74 [-2.51, 1.03]	Mean Difference IV, Random, 95% Cl
Study or Subgroup 2.1.1 10mg Yaday et al 2019 Nazir et al 2017	10.8 10.8 4.8	Nalbuph <u>m S</u> 34 3.2 39 1.	ine <u>D Tota</u> 4 29 5 30	(<u>Mean</u> 9 11.58 0 14.62	3.56 1.73	<u>Total</u> 28 30	Weight 4.7% 5.2%	Mean Difference IV. Random, 95% CI -0.74 [-2.51, 1.03] -9.73 [-10.55, -8.91]	Mean Difference IV. Random, 95% Cl
<u>Study or Subgroup</u> 2.1.1 10mg Yadav et al 2019 Nazir et al 2017 Mohamed et al 2021	Mea 10.8 4.8 11	Nalbuph <u>m S</u> 34 3.2 39 1. .3 3.	ine <u>D Tota</u> 4 29 5 30 4 30	(<u>Mean</u> 3 11.58 0 14.62 0 12.1	3.56 1.73 3.6	28 30 30	4.7% 5.2% 4.7%	Mean Difference <u>IV, Random, 95% Cl</u> -0.74 [-2.51, 1.03] -9.73 [-10.55, -8.91] -0.80 [-2.57, 0.97]	Mean Difference IV. Random, 95% Cl
Study or Subgroup 2.1.1 10mg Yadav et al 2019 Nazir et al 2017 Mohamed et al 2021 Mehta et al 2022	10.8 10.8 4.8 11 10.8	Nalbuph <u>m S</u> 34 3.2 39 1. .3 3. 39 0.7	ine <u>D Tota</u> 5 3(4 3(7 3(9 11.58 0 14.62 0 12.1 0 11.26	3.56 1.73 3.6 1	28 30 30 30	4.7% 5.2% 4.7% 5.3%	Mean Difference N, Random, 95% Cl -0.74 [-2.51, 1.03] -9.73 [-10.55, -8.91] -0.80 [-2.57, 0.97] -0.37 [-0.82, 0.08] -0.07	Mean Difference IV. Random, 95% Cl
Study or Subgroup 2.1.1 10mg Yadav et al 2019 Nazir et al 2017 Mohamed et al 2021 Mehta et al 2022 Madhusudhanan et al 2021 Khamis et al 2021	10.8 10.8 4.8 11 10.8 21 9.5 7	Nalbuph <u>m S</u> 34 3.2 39 1. .3 3. 39 0.7 57 1. 57 1.	ine <u>D Tota</u> 4 29 5 30 4 30 7 30 5 30 2 30	0 11.58 0 14.62 0 12.1 0 11.26 0 10.36	3.56 1.73 3.6 1 1.7 2.52	28 30 30 30 30 30	Weight 4.7% 5.2% 4.7% 5.3% 5.2% 5.2%	Mean Difference N, Random, 95% Cl -0.74 [-2.51, 1.03] -9.73 [-10.55, -8.91] -0.80 [-2.57, 0.97] -0.37 [-0.82, 0.08] -0.79 [-1.60, 0.02] -0.79 [-1.60, 0.02]	Mean Difference IV. Random, 95% Cl
Study or Subgroup 2.1.1 10mg Yadav et al 2019 Nazir et al 2017 Mohamed et al 2021 Mehta et al 2022 Madhusudhanan et al 202 Khamis et al 2021	10.8 4.8 11 10.8 21 9.5 7 7	Nalbuph m S 34 3.2 39 1. .3 3. 39 0.7 57 1. .3 1.3 .3 1.3	ine <u>D Tota</u> 4 29 5 30 4 30 7 30 5 30 2 30 4 30	0 11.58 0 14.62 0 12.1 0 11.26 0 10.36 0 13.37	3.56 1.73 3.6 1 1.7 2.53 1.24	28 30 30 30 30 30 30 30	4.7% 5.2% 4.7% 5.3% 5.2% 5.1% 5.2%	Mean Difference <u>N, Random, 95% Cl</u> -0.74 [-2.51, 1.03] -9.73 [-10.55, -8.91] -0.80 [-2.57, 0.97] -0.37 [-0.82, 0.08] -0.79 [-1.60, 0.02] -6.07 [-7.09, -5.05] -1.34 L2 03, -0.65]	Mean Difference N. Random, 95% Cl
Study or Subgroup 2.1.1 10mg Yadav et al 2019 Nazir et al 2017 Mohamed et al 2021 Mehta et al 2022 Madhusudhanan et al 202 Khamis et al 2021 Kalika 2020 Jain et al 2019	10.8 10.8 4.8 11 10.8 21 9.5 7.9 6.2	Nalbuph m S 34 3.2 39 1. .3 3.3 39 0.7 .7 1. .3 1.3 .36 1.3 .36 1.3	ine <u>D Tota</u> 4 29 5 30 4 30 7 30 5 30 2 30 4 30 7 50	9 11.58 9 11.58 0 14.62 0 12.1 0 11.26 0 10.36 0 13.37 0 9.3 0 6.58	3.56 1.73 3.6 1 1.7 2.53 1.34 1.247	Total 28 30 30 30 30 30 30 50	4.7% 5.2% 4.7% 5.3% 5.2% 5.1% 5.2% 5.3%	Mean Difference <u>N, Random, 95% Cl</u> -0.74 [-2.51, 1.03] -9.73 [-10.55, -8.91] -0.80 [-2.57, 0.97] -0.37 [-0.82, 0.08] -0.79 [-1.60, 0.02] -6.07 [-7.09, -5.05] -1.34 [-2.03, -0.65] -0.32 [-0.83, 0.19]	Mean Difference N. Random, 95% Cl
Study or Subgroup 2.1.1 10mg Yaday et al 2019 Nazir et al 2017 Mohamed et al 2021 Mehta et al 2022 Madhusudhanan et al 202 Khamis et al 2021 Kalika 2020 Jain et al 2019 Jadeja et al 2019	10.8 10.8 4.8 11 10.8 21 9.5 7 7.9 6.2 2.4	Nalbuph m S 34 3.2 39 1. 39 0.7 57 1. .3 1.3 36 1. 36 1. 36 1.3 36 1.33 17 0.7	ine <u>D Tota</u> 5 3(5 3(7 3(5 3(7 3(5 3(7 3(7 5(6 3((<u>1 Mean</u>) 9 11.58 0 14.62 0 12.1 0 11.26 0 10.36 0 13.37 0 9.3 0 6.58 0 4.47	3.56 1.73 3.6 1 1.7 2.53 1.34 1.247 1.34	28 30 30 30 30 30 30 30 50 30	Weight 4.7% 5.2% 4.7% 5.3% 5.2% 5.1% 5.2% 5.3% 5.3%	Mean Difference IV, Random, 95% Cl -0.74 [-2.51, 1.03] -9.73 [-10.55, -8.91] -0.80 [-2.57, 0.97] -0.37 [-0.82, 0.08] -0.79 [-1.60, 0.02] -6.07 [-7.09, -5.05] -1.34 [-2.03, -0.65] -0.32 [-0.83, 0.19] -2.00 [-2.55, -1.45]	Mean Difference <u>IV. Random, 95% Cl</u>
Study or Subgroup 2.1.1 10mg Yadav et al 2019 Nazir et al 2017 Mohamed et al 2021 Madhusudhanan et al 202 Khamis et al 2021 Kalika 2020 Jain et al 2019 Jadeja et al 2019 Imran-Ul-Hassan et al 20	10.8 4.8 111 10.8 21 9.5 7 7.9 6.2 2.4 20 8.1	Nalbuph <u>m S</u> 34 3.2 39 1. 39 1. 39 0.7 57 1. 3 1.3 30 1. 30 1. 31.3 30 1. 31.3 30 1. 31.3 30 1. 31.3 32 1. 33 1.3 30 1. 31.3 32 1. 33 1.3 30 1. 31.3 32 1. 33 1.3 30 1. 31.3 32 1. 33 1. 33 1. 33 1. 34 1.3 35 1. 37 1. 37 1. 37 1. 37 1. 37 1. 37 1. 37 1. 37 1. 37 1. 38 1. 39 0.7 57 1. 31.3 30 1. 31.3 30 1. 31.3 32 1. 31.3 32 1. 31.3 32 1. 31.3 32 1. 32 1. 33 1. 33 1. 33 1. 33 1. 33 1. 33 1. 33 1. 33 1. 32 1.	ine <u>D Tota</u> 4 29 5 30 4 30 7 30 5 30 2 30 4 30 7 50 6 30 4 24	(Mean 11.58 14.62 12.1 11.26 10.36 13.37 9.3 0.6.58 0.4.47 13.47	3.56 1.73 3.6 1 1.7 2.53 1.34 1.247 1.34 4.77	Total 28 30 30 30 30 30 30 50 30 24	Weight 4.7% 5.2% 4.7% 5.3% 5.2% 5.1% 5.2% 5.3% 4.4%	Mean Difference IV, Random, 95% Cl -0.74 [-2.51, 1.03] -9.73 [-10.55, -8.91] -0.80 [-2.57, 0.97] -0.37 [-0.82, 0.08] -0.79 [-1.60, 0.02] -6.07 [-7.09, -5.05] -1.34 [-2.03, -0.65] -0.32 [-0.83, 0.19] -2.00 [-2.55, -1.45] -5.35 [-7.44, -3.26]	Mean Difference <u>IV. Randem, 95% Cl</u> -
Study or Subgroup 2.1.1 10mg Yadav et al 2019 Nazir et al 2017 Mohamed et al 2021 Mehta et al 2022 Madhusudhanan et al 202 Khamis et al 2021 Kalika 2020 Jain et al 2019 Jadeja et al 2019 Imran-Ul-Hassan et al 20 Gupta et al 2016	10.8 10.8 4.8 11 10.8 21 9.5 7 7.9 6.2 2.4 20 8.1 9.5	Nalbuph n S 34 3.2 39 1. 33 3. 39 0.7 57 1. 3 1.3 36 1. 36 1. 36 1. 36 1. 37 0.7 12 2.1 57 1. 57 1.	ine <u>D Tota</u> 5 3(4 3(7 3(5 3(5 3(4 3(7 5(6 3(4 2(5 3(5 3(5 3(5 3(5 3(6 3())))))))))))))))))))))))))))))))))))	I Mean 9 11.58 0 14.62 0 12.1 0 11.26 0 10.36 0 13.37 0 9.3 0 6.58 0 4.47 4 13.47 0 10.36	3.56 1.73 3.6 1 1.7 2.53 1.34 1.247 1.34 4.77 1.7	Total 28 30 30 30 30 30 30 50 30 24 30	Weight 4.7% 5.2% 4.7% 5.3% 5.2% 5.2% 5.3% 5.3% 4.4% 5.2%	Mean Difference IV, Random, 95% Cl -0.74 [-2.51, 1.03] -9.73 [-10.55, -8.91] -0.80 [-2.57, 0.97] -0.37 [-0.82, 0.08] -0.79 [-1.60, 0.02] -0.79 [-1.60, 0.02] -1.34 [-2.03, -0.65] -0.32 [-0.83, 0.19] -2.00 [-2.55, -1.45] -5.35 [-7.44, -3.26] -0.79 [-1.60, 0.02]	Mean Difference <u>IV. Random, 95% Cl</u>
Study or Subgroup 2.1.1 10mg Yadav et al 2019 Nazir et al 2017 Mohamed et al 2021 Mehta et al 2022 Madhusudhanan et al 202 Khamis et al 2021 Kalika 2020 Jain et al 2019 Jadeja et al 2019 Imran-UI-Hassan et al 20 Gupta et al 2020	10.8 4.8 11. 10.8 21 9.5 6.2 2.4 20 8.1 9.5 6.5	Nalbuph n S 34 3.2 39 1. .3 3. 39 0.7 57 1. .3 1.3 36 1. 26 1.33 17 0.7 12 2.1 57 1. 57 2.3 16 2.3 17 1. 18 2.2 19 2.2 19 2.2 10 2.	ine <u>D Tota</u> 5 3(5 3(5 3(7 3(5 3(5 3(1 3(6 3(4 2) 5 3(4 2) 5 3(4 3())))))))))))))))))))))))))))))))))))	(Mean 11.58 14.62 14.62 12.1 11.26 11.26 10.36 13.37 9.3 6.58 4.47 4.13.47 10.36 1.367 1.347 10.36 1.347 10.36 1.347	3.56 1.73 3.6 1 1.7 2.53 1.34 1.247 1.34 4.77 1.7 2.27	Total 28 30 30 30 30 30 30 50 30 24 30 30	Weight 4.7% 5.2% 4.7% 5.3% 5.1% 5.2% 5.3% 4.4% 5.2% 5.2% 5.2%	Mean Difference N, Random, 95% Cl -0.74 [-2.51, 1.03] -9.73 [-10.55, -8.91] -0.80 [-2.57, 0.97] -0.37 [-0.82, 0.08] -0.79 [-1.60, 0.02] -0.79 [-1.60, 0.02] -0.32 [-0.83, 0.19] -2.00 [-2.55, -1.45] -0.32 [-7.44, -3.26] -0.79 [-1.60, 0.02] -6.00 [-7.25, -4.91] -0.00 [-7.25, -4.91]	Mean Difference <u>IV. Random, 95% Cl</u>
Study or Subgroup 2.1.1 10mg Yadav et al 2019 Nazir et al 2017 Mohamed et al 2021 Mehta et al 2022 Madhusudhanan et al 202 Khamis et al 2021 Kalika 2020 Jain et al 2019 Jadeja et al 2019 Imran-UI-Hassan et al 20 Gupta et al 2016 Farrukh et al 2020 Das et al 2017	10.8 4.8 11. 10.8 21 9.5 6.2 2.4 20 8.1 2.4 20 8.1 5.4 15.4	Nalbuph m S 34 3.2 39 1. .3 3.3 39 0.7 .3 1.3 36 1. 26 1.33 36 1.33 16 1.33 16 2.34 16 2.34 16 2.34	ine <u>D Tota</u> 4 29 5 30 4 30 7 30 5 30 2 30 4 30 7 50 6 30 4 24 5 30 4 24 5 30 4 30 7 50 6 30 4 30 7 50 6 30 4 30 7 50 6 30 4 30 7 50 8 5	(<u>Mean</u>) 11.58 14.62	3.56 1.73 3.6 1.77 2.53 1.34 1.247 1.34 4.77 1.7 2.27 4.08	Total 28 30 30 30 30 30 30 30 30 30 24 30 30 30 30	4.7% 5.2% 4.7% 5.3% 5.2% 5.3% 5.3% 4.4% 5.2% 5.0% 4.7%	Mean Difference N, Random, 95% Cl -0.74 [-2.51, 1.03] -9.73 [-10.55, -8.91] -0.80 [-2.57, 0.97] -0.37 [-0.82, 0.08] -0.79 [-1.60, 0.02] -6.07 [-7.09, -5.05] -1.34 [-2.03, -0.65] -0.32 [-0.83, 0.19] -2.00 [-2.55, -1.45] -5.35 [-7.44, -3.26] -0.79 [-1.60, 0.02] -6.08 [-7.25, -4.91] -0.64 [-2.31, 1.03] -0.64 [-2.31, 1.03]	Mean Difference <u>IV. Random, 95% Cl</u>
Study or Subgroup 2.1.1 10mg Yadav et al 2019 Nazir et al 2017 Mohamed et al 2021 Mehta et al 2022 Madhusudhanan et al 202 Khamis et al 2021 Kalika 2020 Jain et al 2019 Jadeja et al 2019 Imran-UI-Hassan et al 20 Gupta et al 2016 Farrukh et al 2020 Das et al 2017 Arish et al 2021	1 Mea 10.8 4.8 11 10.8 21 9.5 6.2 4.2 8.1 9.5 6.5 15.4 5 6.5 15.4 5 6 6 6 5 6 6 6 6 6 6 6 6 6 6 6 6 6	Nalbuph n S 34 3.2 39 1. 33 3. 39 0.7 57 1. 33 1.3 36 1. 36 1.3 36 1. 36 1.3 37 0.7 12 2.1 57 1. 56 2.3 46 3.4 57 2.8 50 2.0 50 2.2 50 2.5 50 2.5	ine <u>D Tota</u> 4 29 5 30 4 30 7 30 5 30 2 30 4 30 7 50 6 30 4 20 5 30 4 30 7 50 6 30 4 30 7 50 6 30 4 30 7 50 6 30 4 30 7 50 8 30 7 50 8 30 7 30 8 30 7 30 8 3	(Mean 9 11.58 9 11.58 0 14.62 0 12.1 0 11.26 0 10.36 0 13.37 9 .3 0 6.58 0 4.47 1 10.36 0 4.47 1 10.36 0 12.64 9 16.1 5 8.34 0 9 1	3.56 1.73 3.6 1.77 2.53 1.34 1.247 1.34 4.77 1.7 2.27 4.08 3.81 1.92	Total 28 30 30 30 30 30 50 30 24 30 30 30 30 30 30 30 30 30 30 30 30 30	4.7% 5.2% 4.7% 5.3% 5.2% 5.3% 5.3% 5.3% 5.3% 5.3% 5.2% 5.0% 4.7% 4.8%	Mean Difference N, Random, 95% Cl -0.74 [-2.51, 1.03] -9.73 [-10.55, -8.91] -0.80 [-2.57, 0.97] -0.37 [-0.82, 0.08] -0.79 [-1.60, 0.02] -6.07 [-7.09, -5.05] -1.34 [-2.03, -0.65] -0.32 [-0.83, 0.19] -2.00 [-2.55, -1.45] -5.35 [-7.44, -3.26] -0.79 [-1.60, 0.02] -6.08 [-7.25, -4.91] -0.64 [-2.31, 1.03] -3.14 [-4.74, -1.54] -3.25 [-2.22, -2.41]	Mean Difference <u>IV. Random, 95% Cl</u>
Study or Subgroup 2.1.1 10mg Yaday et al 2019 Nazir et al 2017 Mohamed et al 2021 Mehta et al 2022 Madhusudhanan et al 202 Khamis et al 2021 Kalika 2020 Jain et al 2019 Jadeja et al 2019 Imran-UI-Hassan et al 20 Gupta et al 2016 Farrukh et al 2020 Das et al 2017 Arish et al 2021 Annamalai et al 2021	10.8 10.8 4.8 11 10.8 21 9.5 6.2 2.4 20 8.1 2.4 20 8.1 9.5 6.5 15.4 5 6.2 15.4 13.4 13.4	Nailburgh m S 34 3.2 39 1. 39 1. 39 0.7 7 1. 36 1.33 36 1.33 36 1.33 36 1.33 36 1.33 36 1.33 36 1.33 36 1.33 36 1.33 36 1.33 36 2.33 36 2.33 36 2.33 37 1.33 38 2.33 39 3.34 30 3.34	ine D Tota 4 29 5 30 4 30 7 30 5 30 5 30 6 30 6 30 6 30 6 30 6 30 6 30 6 30 7 30 8 30 7 30 7 30 7 30 8 300	(1 Mean 9 11.58 0 14.62 0 12.1 0 11.26 0 10.36 0 13.37 0 9.3 0 6.58 0 4.47 10.36 0 4.47 10.36 0 12.64 9 16.1 5 8.34 0 9.1 16.67	Control SD 3.56 1.73 3.6 1.7 2.53 1.34 1.247 1.34 4.77 1.7 2.27 4.08 3.81 1.02 3.81 1.02 5.35	Total 28 30 30 30 30 30 50 30 24 30 30 30 30 30 39 34 30 26	Weinht 4.7% 5.2% 4.7% 5.3% 5.2% 5.2% 5.3% 5.3% 5.3% 5.3% 4.4% 5.0% 4.7% 4.8% 5.3%	Mean Difference N, Random, 95% Cl -0.74 [-2.51, 1.03] -9.73 [-10.55, -8.91] -0.80 [-2.57, 0.97] -0.37 [-0.82, 0.08] -0.79 [-1.60, 0.02] -6.07 [-7.09, -5.05] -1.34 [-2.03, -0.65] -0.32 [-0.83, 0.19] -2.00 [-2.55, -1.45] -5.35 [-7.44, -3.26] -0.79 [-1.60, 0.02] -6.08 [-7.25, -4.91] -0.64 [-2.31, 1.03] -3.14 [-4.74, -1.54] -2.87 [-3.33, -2.41] -3.14 [-5.70, -0.58]	Mean Difference <u>IV. Random, 95% Cl</u>
Study or Subgroup 2.1.1 10mg Yaday et al 2019 Nazir et al 2017 Mohamed et al 2021 Mehta et al 2022 Madhusudhanan et al 202 Kalika 2020 Jain et al 2019 Jadeja et al 2019 Imran-Ul-Hassan et al 20 Gupta et al 2016 Farrukh et al 2020 Das et al 2017 Arish et al 2021 Annamalai et al 2018 Aggarwal et al 2021 Abajdullab et al 2021	10.8 10.8 4.8 11 10.8 21 9.5 7 7.9 7.9 7.9 7.9 7.9 7.9 7.9 7.9 7.9 7	Nailburgh m S 34 3.2 39 1. 39 1.3 39 0.7 57 1. 36 1.33 36 1.33 36 1.33 36 1.33 36 1.33 36 1.33 36 1.33 36 1.33 36 1.33 36 1.33 36 2.33 36 2.33 36 2.33 36 2.33 37 1.33 36 3.42 37 3.34 37 3.34 38 0.7 37 3.34 37 3.34 38 0.7 37 3.34 38 0.7 39 0.2 39 0.2 39 0.2	ine D Tota 4 29 5 30 4 30 7 30 5 30 5 30 7 30 6 30 6 30 4 29 30 4 30 7 30 4 30 7 30 4 30 7 30 4 30 7 30 4 30 4 30 7 30 4 4 30 4 4 30 4 4 30 4 4 4 4 4 4 4 4	(Mean 9 11.58 0 14.62 0 12.1 0 11.26 0 10.36 0 10.36 0 13.37 0 9.3 0 6.58 0 4.47 4 13.47 0 10.36 0 12.64 9 16.1 5 8.34 0 9.1 0 16.67 8 13.47	Control SD 3.56 1.73 3.6 1 1.73 2.53 1.34 1.247 1.34 4.77 2.27 4.08 3.81 1.02 5.35 4.77	Total 28 30 30 30 30 30 50 30 24 30 30 39 34 30 39 34 30 32 6 48	Weinht 4.7% 5.2% 4.7% 5.2% 5.2% 5.2% 5.3% 4.4% 5.3% 4.4% 5.0% 4.7% 4.8% 5.3% 4.8% 5.3%	Mean Difference N, Random, 95% Cl -0.74 [-2.51, 1.03] -9.73 [-10.55, -8.91] -0.80 [-2.57, 0.97] -0.37 [-0.82, 0.08] -0.79 [-1.60, 0.02] -6.07 [-7.09, -5.05] -1.34 [-2.03, -0.65] -0.32 [-0.83, 0.19] -2.00 [-2.55, -1.45] -5.35 [-7.44, -3.26] -0.79 [-1.60, 0.02] -6.08 [-7.25, -4.91] -0.64 [-2.31, 1.03] -3.14 [-4.74, -1.54] -2.87 [-3.33, -2.41] -3.14 [-5.70, -0.58] -5.35 [-6.83, -3.87]	Mean Difference <u>IV. Randem, 95% Cl</u>
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Study or Subgroup 2.1.1 10mg Yaday et al 2019 Nazir et al 2017 Mohamed et al 2021 Mehta et al 2022 Madhusudhanan et al 202 Kalika 2020 Jain et al 2019 Jadeja et al 2019 Imran-Ul-Hassan et al 20 Gupta et al 2010 Das et al 2017 Arish et al 2020 Das et al 2017 Arish et al 2021 Annamalai et al 2018 Aggarval et al 2021 Subtotal (95% Cl) Heterogeneih: Tau ^a = 6.4 Test for overall effect: Z = 2.1.2 20mg Kalika 2020 Abdelhand et al 2016 Abdelhamid et al 2018	10.8 10.8 4.8 11 10.8 21 9.5 6.2 2.4 20 8.1 15.4 5 6.2 15.4 5 6.2 15.4 5 6.2 13.5 8.1 2; Chi ^P = 6 4.57 (P < 0 7.5 6.2 13.5 8.1 13.5 6.2 13.5 8.1 13.5 6.2 13.5 8.1 15.4 5 6.2 13.5 8.1 15.4 5 6.2 13.5 8.1 15.4 5 6.2 13.5 8.1 15.4 5 6.2 13.5 8.1 15.4 5 6.2 13.5 8.1 15.4 5 6.2 13.5 8.1 15.4 5 6.2 13.5 8.1 15.4 5 6.2 13.5 8.1 13.5 8.5 7.5 7.5 8.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7	Nalbuph m S 34 3.2 39 1. 3 3 1. 3 1. 3 1. 3 1. 3 1. 3 1. 3 1.	ine D Tota 4 21 5 31 5 31 5 31 5 31 5 31 5 31 5 31 5 31 7 31 30 31 31 31 32 32 33 <td>I Mean 0 11.58 0 14.62 0 12.1 0 11.26 0 10.36 0 13.37 0 9.3 0 4.47 1 10.36 0 12.64 0 16.67 3 16.1 5 3.347 5 9.0000 9.3 9.18 5 9.965</td> <td>Control SD 3.56 1.73 3.66 1.73 3.6 1 1.7 2.53 1.34 1.247 1.34 4.77 1.7 2.27 4.08 3.81 1.02 5.35 4.77 01); P= \$ 1.34 1.37 2.66</td> <td>Total 28 30 34 30 26 48 549 30 28 30 28 30 28 30 148</td> <td>Weight 4.7% 5.2% 4.7% 5.2% 5.2% 5.3% 4.4% 5.2% 5.3% 4.4% 5.3% 4.1% 4.9% 84.4% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3</td> <td>Mean Difference IV, Random, 95% Cl -0.74 [-2.51, 1.03] -9.73 [-10.55, -8.91] -0.80 [-2.57, 0.97] -0.37 [-0.82, 0.08] -0.79 [-1.60, 0.02] -0.79 [-1.60, 0.02] -0.32 [-0.83, 0.19] -2.00 [-2.55, -1.45] -5.35 [-7.44, -3.26] -0.79 [-1.60, 0.02] -6.08 [-7.25, -4.91] -0.64 [-2.5, -1.45] -3.14 [-4.74, -1.54] -3.14 [-5.70, -0.58] -5.35 [-6.83, -3.87] -2.90 [-4.15, -1.66] -1.64 [-2.49, -0.79] -0.54 [-1.11, 0.03] -0.75 [-1.58, 0.09]</td> <td>Mean Difference <u>N. Randem, 95% Cl</u></td>	I Mean 0 11.58 0 14.62 0 12.1 0 11.26 0 10.36 0 13.37 0 9.3 0 4.47 1 10.36 0 12.64 0 16.67 3 16.1 5 3.347 5 9.0000 9.3 9.18 5 9.965	Control SD 3.56 1.73 3.66 1.73 3.6 1 1.7 2.53 1.34 1.247 1.34 4.77 1.7 2.27 4.08 3.81 1.02 5.35 4.77 01); P= \$ 1.34 1.37 2.66	Total 28 30 34 30 26 48 549 30 28 30 28 30 28 30 148	Weight 4.7% 5.2% 4.7% 5.2% 5.2% 5.3% 4.4% 5.2% 5.3% 4.4% 5.3% 4.1% 4.9% 84.4% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3	Mean Difference IV, Random, 95% Cl -0.74 [-2.51, 1.03] -9.73 [-10.55, -8.91] -0.80 [-2.57, 0.97] -0.37 [-0.82, 0.08] -0.79 [-1.60, 0.02] -0.79 [-1.60, 0.02] -0.32 [-0.83, 0.19] -2.00 [-2.55, -1.45] -5.35 [-7.44, -3.26] -0.79 [-1.60, 0.02] -6.08 [-7.25, -4.91] -0.64 [-2.5, -1.45] -3.14 [-4.74, -1.54] -3.14 [-5.70, -0.58] -5.35 [-6.83, -3.87] -2.90 [-4.15, -1.66] -1.64 [-2.49, -0.79] -0.54 [-1.11, 0.03] -0.75 [-1.58, 0.09]	Mean Difference <u>N. Randem, 95% Cl</u>
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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 metaanalysis 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.

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