

# Nalbuphine as an adjuvant to bupivacaine in ultrasound-guided brachial plexus blockade: A meta-analysis of randomized and controlled trials



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Submission: 30-07-2023

Revision: 04-12-2023

Publication: 01-01-2024

## ABSTRACT

The brachial plexus block is a flexible and reliable regional anesthetic method with a wide range of applications. In this study, we aim to determine whether nalbuphine in combination with the local anesthetic bupivacaine could increase the efficacy and duration of analgesia during ultrasound-guided blockade of the brachial plexus. Seven randomized and controlled trials involving 416 patients were included after searching PubMed, Google, and Web of Science. Results of the studies were then retrieved and effect sizes were calculated using Review Manager 5. Duration of analgesia was significant heterogeneity between studies ( $P < 0.00001$ ,  $I^2 = 96\%$ ). A random-effects model was used, and there was significant heterogeneity between studies in the duration of analgesia. A significant difference was found between groups (standard mean difference [MD] 6.27, confidence interval [CI] [4.40–8.60],  $P < 0.001$ ). Duration of motor block was also significant heterogeneity between studies ( $P < 0.00001$ ,  $I^2 = 98\%$ ). A random-effects model was used, and there was significant heterogeneity between studies in the duration of motor block. A significant difference was found between groups (standard MD 6.27, CI [4.01–8.54],  $P < 0.001$ ). In supraclavicular brachial plexus blockade, the duration of analgesia and the duration of motor blockade can be prolonged using nalbuphine as an adjuvant with bupivacaine.

**Key words:** Supraclavicular brachial plexus blockade; Bupivacaine; Nalbuphine; Analgesia

### Access this article online

**Website:**

<http://nepjol.info/index.php/AJMS>

**DOI:** 10.3126/ajms.v15i1.57163

**E-ISSN:** 2091-0576

**P-ISSN:** 2467-9100

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## INTRODUCTION

Brachial plexus block is a practical and reliable regional anesthetic procedure with multiple applications. For some people today, it is an acceptable substitute for general anesthesia. The most widely used regional nerve block for the upper extremities is brachial plexus block, which prevents the unintended effects of anesthetics used in general anesthesia as well as the burden of laryngoscopy and tracheal intubation.<sup>1</sup> Because it provides improved intraoperative and postoperative analgesia, promotes rapid recovery, and avoids typical side effects of general anesthesia such as post-operative nausea and vomiting, brachial plexus block is a suitable substitute for general anesthesia in upper

abdominal procedures.<sup>2</sup> The post-operative analgesic effect of supraclavicular block (SCB), which is now commonly used for arm, forearm, and hand procedures, has been investigated in numerous studies.<sup>3</sup>

Safe procedures for localized blocks are made possible by ultrasound visualization of the anatomical features, as the anesthesiologist can place the needle in the ideal location and observe the flow of local anesthetic in real-time.<sup>4,5</sup> Various drugs have been used as adjuvants to local anesthetics during brachial plexus blockade to prolong the duration of analgesia. Adjuvants can be added to local anesthetics to prolong the onset and duration of blockade, increase patient satisfaction, maintain healthy

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hemodynamics, and reduce the need for post-operative analgesics.<sup>6</sup>

Intrathecal morphine served as a precursor when an opioid was first added to a local anesthetic for spinal anesthesia in clinical use in 1979. Opioids and local anesthetics are administered together to improve analgesia during and after surgery.<sup>7</sup> While nalbuphine is readily available and free from adverse effects such as nausea, vomiting, pruritus, and respiratory depression, many opioids, including morphine, fentanyl, and other opioids, fall under the Narcotics Act and are therefore not readily available in many hospitals in India.<sup>8</sup>

Nalbuphine is an opioid agonist-antagonist structurally related to oxymorphone and naloxone. It binds to opioid receptors, acts as an antagonist at the mu-receptor and an agonist at the kappa-receptor, and is used clinically primarily in post-operative pain management as a bolus, continuous infusion, and patient-controlled analgesia.<sup>9,10</sup> It is designed to provide analgesia without the undesirable side effects of agonists such as respiratory depression, unwanted drowsiness, nausea, vomiting, and urine retention. There are few published data comparing the effects of adding nalbuphine and fentanyl as adjuvants to bupivacaine during spinal blockade in lower abdominal surgery.<sup>11-23</sup>

In various models of visceral nociception, nalbuphine, and other agonists have produced significant analgesia.<sup>15</sup> They interact with opiates in complex ways, suggesting both dose-dependent synergy and potent antagonistic effects at higher doses,<sup>16</sup> although their short duration of action is consistent with their lipid solubility and rapid excretion. Therefore, we aimed to determine whether nalbuphine in combination with the local anesthetic bupivacaine could increase the efficacy and duration of analgesia during ultrasound-guided blockade of the brachial plexus.

## MATERIALS AND METHODS

### Setting and study design

This meta-analysis study was conducted in the Department of Anaesthesiology, ERA's, Lucknow Medical University and Hospital, ERA University, Lucknow.

### Identification and methods: search and selection of studies

Articles on brachial plexus block were found independently by the investigators in PubMed, Google, and Web of Science. The search terms were as follows: (brachial plexus block OR SCB OR local anesthetic OR bupivacaine OR adjuvant OR opioid OR nalbuphine AND (onset of sensory OR motor block) AND (duration of motor block

OR duration of analgesia). In addition, references to all articles and reviews were manually searched for additional appropriate studies.

Results were limited to brachial plexus, local anesthetics bupivacaine and nalbuphine, and onset of sensory and motor block, duration of motor block, and duration of analgesia. A total of 238 articles were found in PubMed, Google, and Web of Science. Inclusion criteria for study selection and inclusion were: (1) randomized and controlled trial (RCT); (2) Group NB: Received 0.5% bupivacaine with nalbuphine, and Group B: Received 0.5% bupivacaine with normal saline; (3) published articles; (4) full article in English; (5) studies in animals were excluded from the study. The efficacy and duration of analgesia nalbuphine with bupivacaine and bupivacaine with normal saline in ultrasound-guided brachial plexus blockade were the main concern in the selection of studies.

### Data collection

Data were extracted individually by the authors from the text, figures, or tables of each published article. The above details were collected from the individual studies, that is, Group NB: Received 0.5% bupivacaine with nalbuphine, and Group B: Received 0.5% bupivacaine with normal saline, brachial plexus blockade, onset of sensory motor block, duration of motor block, and duration of analgesia (Table 1).

### Synthesis of the data

The following information was collected for each study: title of article, name of lead author, name of journal, date of publication, name of country, and type of the block.

### Statistical analysis

Review Manager 5.3 (RevMan 5.3), the Cochrane Collaboration, based in London, United Kingdom was used for statistical analysis. The mean difference (MD) and its 95% confidence interval (CI) were used to indicate the time between onset of sensory and motor blockade, the time between motor blockade, and the time between analgesia. Study heterogeneity was assessed using the Q (2) test and the I<sup>2</sup> statistic. We assumed significant heterogeneity and used the random-effects model to calculate the effect size. In addition, we performed a sensitivity analysis to examine the sources of heterogeneity. P=0.05 was considered statistically significant for the effect sizes.

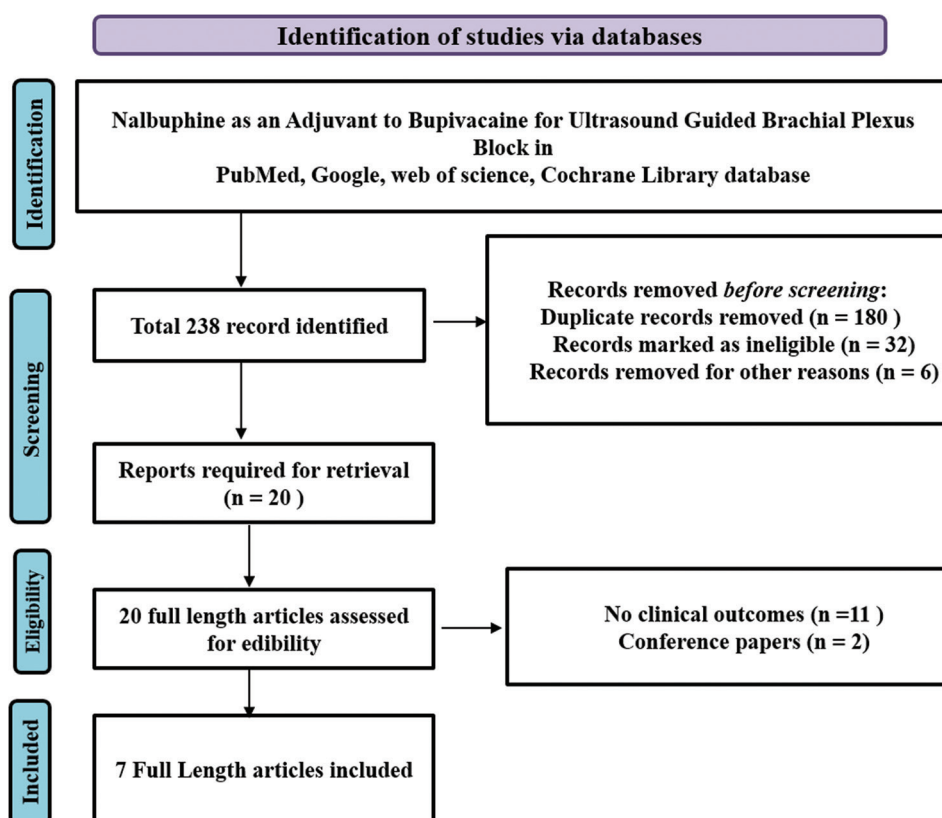
## RESULTS

### Search results

Figure 1 shows the search results for published articles. Two hundred and thirty-eight literature works were initially

**Table 1: Characteristics/details of included studies for meta-analysis**

Studies	Surgery	Measures	Groups (n): Treatment
Abdelhaq and Elramely <sup>17</sup>	Ultrasound-guided supraclavicular brachial plexus block	Duration of analgesia	NB: Received 25 mL (0.5%) bupivacaine with 1 mL nalbuphine 20 mg B: Received 25 mL (0.5%) bupivacaine with 1 mL of normal saline
Gupta et al. <sup>18</sup>	Ultrasound-guided supraclavicular brachial plexus block	Duration of analgesia	NB: Received 20 mL of 0.5% bupivacaine with 1 mL of nalbuphine 10 mg B: Received 20 mL of 0.5% bupivacaine with 1 mL of normal saline
Annamalai and Chandran <sup>19</sup>	Ultrasound-guided supraclavicular brachial plexus block	Duration of analgesia	NB: 25 mL 0.5% bupivacaine with 1 mL nalbuphine 10 mg B: 0.5% bupivacaine with 1 mL normal saline
Mohamed and Gad <sup>20</sup>	Ultrasound-guided supraclavicular brachial plexus block	Duration of sensory and motor blockade	NB: Received 24 mL of 0.5% isobaric bupivacaine with 1 mL nalbuphine 10 mg B: Received 24 mL of 0.5% isobaric bupivacaine with 1 mL normal saline
Mehta et al. <sup>21</sup>	Ultrasound-guided supraclavicular brachial plexus block	Duration of sensory and motor blockade and postoperative analgesia	NB: Received 20 mL 0.5% bupivacaine with 1 mL nalbuphine 10 mg B: Received 20 mL 0.5% bupivacaine with 1 mL normal saline
Mishra et al. <sup>22</sup>	Ultrasound-guided supraclavicular brachial plexus block	Duration of analgesia	NB: Received 29 mL of 0.5% bupivacaine with 1 mL nalbuphine 10 mg B: Received 29 mL of 0.5% bupivacaine 29 mL with 1 mL of 0.9% normal saline
Madhusudhanan et al. <sup>23</sup>	Ultrasound-guided supraclavicular brachial plexus block	Peripheral nerve blocks, with faster onset, longer duration	NB: Received 20 mL of 0.5% bupivacaine with 2 mL nalbuphine 10 mg/mL B: Received 20 mL of 0.5% bupivacaine and 2 mL of normal saline

**Figure 1:** Flow diagram of article searching, screening, eligibility, and included or selection process

looked up and obtained. A total of 212 literature references were reviewed for relevance to the topic, duplicate works, and review articles before being excluded from this meta-analysis. This was done based on the titles and abstracts of

the papers. After reviewing the abstracts of the records, six published articles were also excluded. After abstract and title review, 20 articles were selected for full-text review. Due to the lack of sufficient data and conference papers, many

studies were excluded from the study. Therefore, a total of seven studies were included in the meta-analysis, which included 208 (0.5%) bupivacaine with nalbuphine in the NB group and 208 (0.5%) bupivacaine with normal saline in the B group. Seven publications were finally considered for the meta-analysis, which focused on the onset of sensory and motor blockade, the interval of motor blockade, and the interval of analgesia (Table 1 and Figure 1).<sup>17-23</sup>

### Onset of sensory block

A total of seven studies were evaluated for onset of sensory blockade, including 208 (0.5%) bupivacaine with nalbuphine in the NB group and 208 (0.5%) bupivacaine with normal saline in the B group. All studies reported onset of sensory blockade NB group and B group during brachial plexus blockade. There was significant heterogeneity between studies ( $P < 0.00001$ ,  $I^2 = 89\%$ ). A random-effects model was used, and there was significant heterogeneity between studies in the onset of sensory blockade. A significant difference was found between groups (standard MD  $-0.92$ , CI  $[-1.54-0.30]$ ,  $P = 0.004$ ) (Figure 2).

### Onset of motor block

A total of seven studies were evaluated for onset of motor blockade, including 208 (0.5%) bupivacaine with nalbuphine in the NB group and 208 (0.5%) bupivacaine with normal saline in the B group. All studies reported onset of motor blockade NB group and B group during brachial plexus blockade. There was significant heterogeneity between studies ( $P < 0.00001$ ,  $I^2 = 96\%$ ). A random-effects model was used, and there was significant heterogeneity between studies in the onset of motor blockade. There was no significant difference found between groups (standard MD  $-0.00$ , CI  $[-1.17-1.17]$ ,  $P = 1.00$ ) (Figure 3).

### Duration of motor block

A total of seven studies were evaluated for the duration of motor block, including 208 (0.5%) bupivacaine with nalbuphine in the NB group and 208 (0.5%) bupivacaine with normal saline in the B group. All studies reported duration of motor blockade NB group and B group during brachial plexus blockade. There was significant heterogeneity between studies ( $P < 0.00001$ ,  $I^2 = 98\%$ ). A random-effects model was used, and there was significant heterogeneity between studies in the duration of motor block. A significant difference was found between groups (standard MD  $6.27$ , CI  $(4.01-8.54)$ ,  $P < 0.001$ ) (Figure 4).

### Duration of analgesia

A total of seven studies were evaluated for the duration of analgesia, including 208 (0.5%) bupivacaine with Nalbuphine in the NB group and 208 (0.5%) bupivacaine with normal saline in the B group. All studies reported duration of analgesia NB group and B group during brachial plexus blockade. There was significant heterogeneity between studies ( $P < 0.00001$ ,  $I^2 = 96\%$ ). A random-effects model was used, and there was significant heterogeneity between studies in the duration of analgesia. A significant difference was found between groups (standard MD  $6.27$ , CI  $[4.40-8.60]$ ,  $P < 0.001$ ) (Figure 5).

## DISCUSSION

Meta-analysis is an effective analytical tool for compiling data from studies with low power. This meta-analysis shows that nalbuphine added to a local anesthetic for brachial plexus blockade can decrease the onset of sensory and motor blockade and prolong the duration of motor blockade and the duration of analgesia.

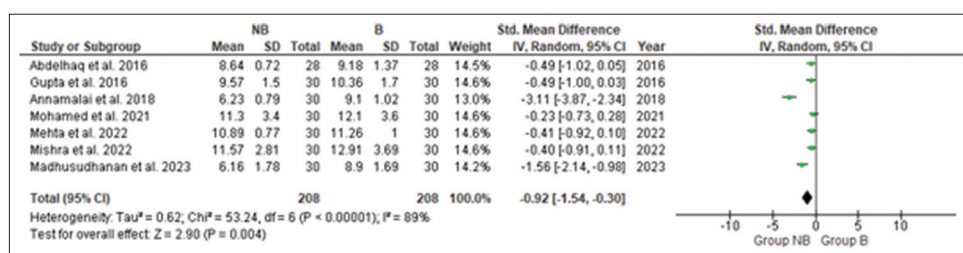


Figure 2: Forest plots of association of onset of sensory block between NB group and B group in brachial plexus block

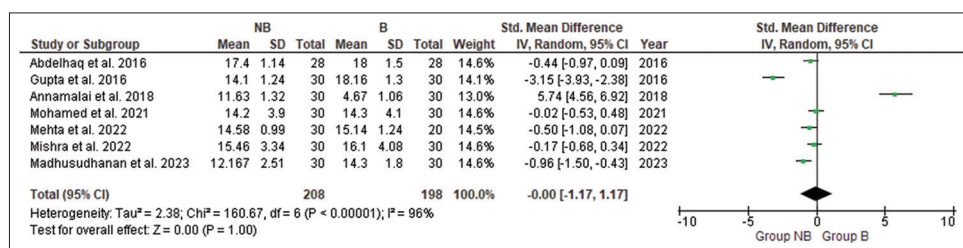


Figure 3: Forest plots of association of onset of motor block between NB group and B group in brachial plexus block

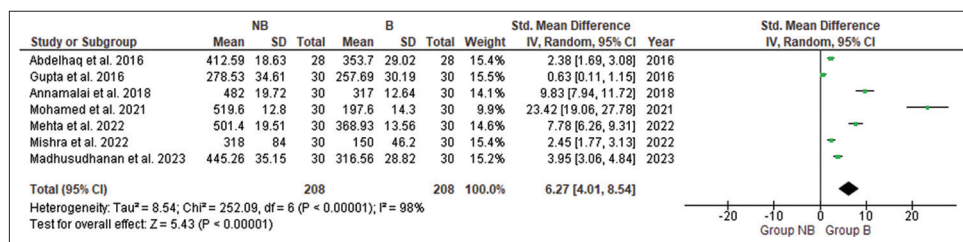


Figure 4: Forest plots of association of duration of motor block between NB group and B group in brachial plexus block

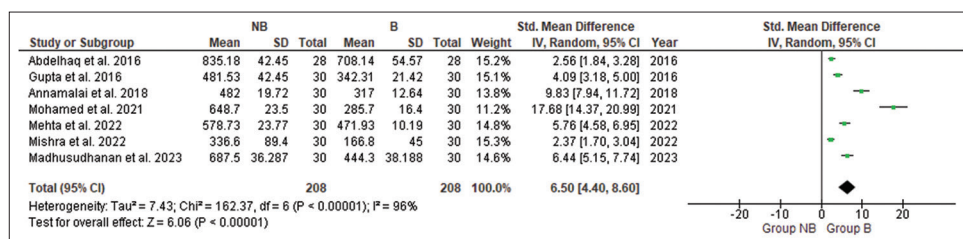


Figure 5: Forest plots of association of duration of analgesia between NB group and B group in brachial plexus block

The primary outcome of this meta-analysis was the post-operative duration of analgesia. The duration of analgesia is considered the gold standard for evaluating the efficacy of a drug. This improvement may be due to the synergistic effect of nalbuphine and bupivacaine. In our study, it was found that the duration of analgesia was significantly longer in the group that received anesthesia with nalbuphine after surgery. Second, the onset of sensory blockade was significantly reduced in the nalbuphine group, whereas the duration of motor blockade was significantly increased in the nalbuphine group. Because nalbuphine is an agonist at K receptors and an antagonist at μ-receptors, itching, nausea, vomiting, and respiratory depression did not occur. This enhancement may be due to the synergistic effect of nalbuphine with bupivacaine. According to Madhusudhanan et al., the average analgesia lasts 42% longer in the nalbuphine group than in the bupivacaine group.<sup>23</sup> According to Gupta et al., the use of nalbuphine as an adjuvant significantly increased the duration of analgesia (481.53±42.45 min) compared to another group (341.31±21.42 min).<sup>18</sup> Mehta et al., showed that the post-operative analgesia duration was significantly longer in the nalbuphine group than in the bupivacaine group (P=0.0001).<sup>21</sup> Compared with the control groups, the duration of analgesia was also significantly prolonged (36–56%).<sup>3,24,25</sup>

An effective method for reducing post-operative discomfort after upper limb surgery is the injection of buprenorphine into the brachial plexus sheath through the supraclavicular approach.<sup>26</sup> According to one study, nalbuphine and tramadol had similar effects when used as an adjuvant to lidocaine during intravenous regional

anesthesia, but nalbuphine was superior to tramadol in prolonging the duration of post-operative analgesia.<sup>27</sup> Another study combining 20 mg of nalbuphine with 25 mL of 0.5% bupivacaine for blockade of the supraclavicular brachial plexus during upper arm surgery reached the same conclusion.<sup>17</sup> Nalbuphine was found to significantly prolong the duration of sensory and motor blockade and the duration of post-operative analgesia. In upper arm procedures, Gupta et al., found that the duration of sensory and motor blockade as well as the duration of analgesia were statistically increased even at lower doses of 10 mg of nalbuphine with 20 mL of 0.5% bupivacaine.<sup>18</sup> They concluded that there were no statistically significant differences in the onset of sensory and motor blocks between the two groups.

A study found that although there was no statistically significant difference between the two groups, the onset of sensory and motor blocks was faster in the nalbuphine group.<sup>21</sup> According to the previous studies, post-operative analgesia and sensory and motor blockade were longer in the nalbuphine group than in the statistically significant control group.<sup>17,18</sup> Mehta et al., found that the duration of sensory and motor block was significantly longer in the nalbuphine group than in the bupivacaine group.<sup>21</sup> According to one study, post-operative analgesia lasted significantly longer in the nalbuphine group than in the control group.

According to Annamalai and Chandran, 0.5% bupivacaine and nalbuphine significantly delayed the development of sensory and motor block.<sup>19</sup> They also showed that the duration of analgesia was significantly longer in the nalbuphine plus bupivacaine group (482±30.6 min)

than in the bupivacaine group ( $317 \pm 23.7$  min).<sup>19</sup> A study demonstrated that supraclavicular blockade during upper arm procedures using 20 mg nalbuphine as an adjuvant to 25 mL 0.5% bupivacaine significantly prolonged both the duration of sensory and motor block and the duration of analgesia.<sup>20</sup>

A study showed that the post-operative analgesic effects of tramadol and nalbuphine when administered epidurally in patients undergoing orthopaedic surgery of the lower limbs. They concluded that the nalbuphine group was superior in terms of greater surgical analgesia, lower incidence of adverse effects, and fewer problems.<sup>28</sup> Another study found that the duration of effective analgesia was prolonged in the morphine group and the morphine-nalbuphine group when 60 patients scheduled for cesarean section under spinal anesthesia received 0.1 mg morphine, 1 mg nalbuphine, or 0.1 mg morphine with 1 mg nalbuphine in addition to 10 mg 0.5% bupivacaine.<sup>29</sup> Gomaa et al., found no statistically significant difference between the two groups when they compared the effects of intrathecal nalbuphine and fentanyl on early post-operative analgesia in 60 patients undergoing elective cesarean section under spinal anesthesia.<sup>30</sup> The used nalbuphine (preservative-free) 0.8 mg as an adjuvant to intrathecal hyperbaric bupivacaine (0.5%) in a series of lower abdominal organ and lower limb surgeries and compared its post-operative analgesic effect under spinal anesthesia with that of hyperbaric bupivacaine (0.5%) alone.<sup>31</sup> The different dosages of intrathecally administered nalbuphine at 0.2 mg, 0.8 mg, and 1.6 mg in 90 obstetric patients undergoing cesarean section and found that 0.8 mg was the most effective dosage.<sup>32</sup> 0.4 mg of nalbuphine is the most effective dose that prolongs the duration of analgesia in the early post-operative period without increasing the risk of side effects. The use of nalbuphine as an adjuvant to 0.5% hyperbaric bupivacaine in spinal anesthesia.<sup>9</sup> They therefore recommended that 0.4 mg of nalbuphine be administered intrathecally along with 12.5 mg of 0.5% hyperbaric bupivacaine for spinal anesthesia in patients undergoing orthopedic lower limb procedures.<sup>9</sup> The effects of tramadol and nalbuphine as adjuvants to lidocaine in intravenous regional anesthesia, the effects of both drugs were equivalent. Tramadol was found to be less effective than nalbuphine in prolonging postoperative analgesia time.<sup>27</sup>

When interpreting the results of the meta-analysis, the numerous limitations should be considered. In addition, a number of limitations must be considered when interpreting our results. First, a total of only seven studies — each with a sample size of fewer than 61 patients —

were included in this meta-analysis; therefore, our results may be biased by small study effects. The type and dosage of local anesthetics and the dosage of nalbuphine vary among the included studies, which may more or less affect the veracity of pooling effects. Second, there are some clinical heterogeneities among the included studies. Third, although the combination of local anesthetics with adjuvants is currently a hot topic, further research is needed to determine the best nalbuphine doses because of the small number of included studies.

## CONCLUSION

The duration of analgesia and the duration of motor block can be prolonged by using nalbuphine as an adjuvant with bupivacaine in supraclavicular brachial plexus blockade. In addition, nalbuphine shortened the onset of sensory and motor blockade. In the meantime, further high-quality RCTs with large samples are needed to increase the credibility found in the current meta-analysis.

## ACKNOWLEDGMENT

None.

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**Authors' Contributions:**

**RK**- Definition of intellectual content, Literature survey, Prepared first draft of manuscript, implementation of study protocol, literature search, identification, data analysis, manuscript preparation, and submission of article; **AJ**- manuscript preparation, editing, and manuscript revision.

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**Source of Funding:** None, **Conflicts of interest:** The authors declare that the study was conducted in the absence of any commercial or financial relationships that could pose as a potential conflict of interest.