INPLASY PROTOCOL

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None declared.

Efficacy and safety of nalbuphine as a local anaesthetic adjuvant for brachial plexus block: a systematic review and meta-analysis of randomized trials

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Review question / Objective: **This systematic review and meta-analysis compare the efficacy and safety of brachial plexus block with and without nalbuphine on duration of analgesia as a primary outcome, as well as other block characteristics, analgesic outcomes and side effects-related outcomes following single-injection brachial plexus block for upper extremity surgery.**
Eligibility criteria: **Inclusion criteria: (1) RCTs that had been published, (2) Trials comparing the combinations of perineural nalbuphine with local anesthetics to local anesthetics alone and (3) a population of patients undergoing upper extremity surgical procedures (elbow, forearm, and hand) under a block of the brachial plexus. When those trials did not report the following at least one of outcomes: sensory block onset, motor block onset, sensory block duration, motor block duration, and duration of analgesia, those would be excluded.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 March 2022 and was last updated on 14 March 2022 (registration number INPLASY202230064).

INTRODUCTION

Review question / Objective: **This systematic review and meta-analysis compare the efficacy and safety of brachial plexus block with and without nalbuphine on duration of analgesia as a primary outcome, as well as other block characteristics, analgesic outcomes and side effects-related outcomes following single-injection brachial plexus block for upper extremitysurgery.**

Condition being studied: **Peripheral nerve blocks using local anesthetics are the most commonly used for limb surgery as better pain relief. However, the primary drawback of the single-shot peripheral nerve**

blockade is its limited duration of action and, especially, be weakened during postoperative analgesia. Anesthetists have found that adding perineural adjuncts to local anesthetics is a technically simple strategy to extend the benefits beyond the duration of commonly available local anesthetics. Nalbuphine is wildly used as adjuvant to local anesthetic for various regional anesthetic techniques to extend duration of analgesia by different routes, including brachial plexus block. Nalbuphine has an agonistic effect at kappa opioid receptors and an antagonistic effect at mu opioid receptors and is considered safer than pure agonist opioid as it has limited effect on respiration when added the dose above 30 mg. However, data comparing the perineural use the combination of nalbuphine with local anesthetics to local anesthetics alone are inconsistent and there haven't been meta-analysis assessed efficacy and safety of nalbuphine as adjuncts yet.

METHODS

Search strategy: Two of the authors independently searched the electronic databases including MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Clinical Trials, Cochrane Database of Systematic Reviews, Web of Science, Scopus, PubMed and EBSCO. The following population search terms were applied: (1) brachial plexus block or nerve block (2) nalbuphine. The search parameters included a combination of free text, Medical Subject Headings and EMTREE terms. In addition, the authors searched Google Scholar (Google, Mountain View, CA) for any relevant trials not identified using the strategy described above.

Participant or population: A population of patients undergoing upper extremity surgical procedures (elbow, forearm, and hand) under a block of the brachial plexus.

Intervention: Combination of nalbuphine and local anesthetics.

Comparator: Local anesthetics alone.

Study designs to be included: Randomized controlled trials (RCTs) will be included.

Eligibility criteria: Inclusion criteria: (1) RCTs that had been published, (2) Trials comparing the combinations of perineural nalbuphine with local anesthetics to local anesthetics alone and (3) a population of patients undergoing upper extremity surgical procedures (elbow, forearm, and hand) under a block of the brachial plexus. When those trials did not report the following at least one of outcomes: sensory block onset, motor block onset, sensory block duration, motor block duration, and duration of analgesia, those would be excluded.

Information sources: Electronic databases.

Main outcome(s): Duration of analgesia.

Additional outcome(s): Sensory and motor block characteristics, side effects-related outcomes and block-related complications.

Quality assessment / Risk of bias analysis: The risk of bias in the included studies was evaluated using the Cochrane Collaboration's 'Risk of bias' tool, as implemented in Review Manager (RevMan, http://www.cochrane.org). Two authors independently screened, reviewed, and scored the items for each trial using this method and extracted data for analysis. Disagreements with scoring or extracted data were resolved through discussion with another author.

Strategy of data synthesis: Meta-analyses were performed with the assistance of Review Manager software (RevMan version 5.3.5; Copenhagen, Denmark, The Nordic Cochrane Centre, The Cochrane Collaboration 2014). This software estimates the weighted mean differences for continuous data and risk ratio for categorical data between groups, with an overall estimate of the pooled effect. We decided to pool data for a particular outcome if ≥3 trials reported this outcome. The I2 coefficient was used to evaluate heterogeneity with predetermined thresholds for low (25%–49%), moderate

(50%–74%), and high (>75%) levels.27 A random-effects model was applied in the event of moderate or high heterogeneity; otherwise, a fixed effects model was used.

Subgroup analysis: We will consider subgroups such as different dose of nalbuphine.

Sensitivity analysis: When heterogeneity was moderate or high, we used metaregression analysis (mixed-effects modeling) and subgroup analysis to explore whether the primary outcome results were associated with ≥1 clinically important covariates that could potentially influence the duration of analgesia. These covariates included the following: (1) block guidance technique (ultrasound/nerve stimulation/ anatomic landmarks/ nerve stimulation + ultrasound); (2) type of local anesthetic used (long/intermediate acting); and (3) dose of local anesthetic used. Meta-regression was performed if ≥3 trials were present within the covariate group. We also used sensitivity analysis when meta-regression on a specific covariate was not feasible because of the limited number of trials (≤3).

Country(ies) involved: China.

Keywords: nalbuphine; Brachial plexus block; analgesia; Peripheral nerve blocks.

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