

INPLASY PROTOCOL

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Corresponding author:
Hong Liu

liuhong@stu.cdutcm.edu.cn

Author Affiliation:
Hospital of Chengdu
University of Traditional Chi

Support: Chengdu University
of TCM

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submission:** Preliminary
searches.

Conflicts of interest:
All authors declare no
conflicts of interest.

INTRODUCTION

Objectives / Review question: Participant: (1) RCTs; (2) receive DEX as an adjuvant to local anesthetic in comparison with local anesthetic alone for local wound infiltration anesthesia; Intervention: Dexmedetomidine as local anesthetic adjuvant for wound

Efficacy and Safety of Dexmedetomidine as an Adjuvant to Local Wound Infiltration Anesthesia: A meta-analysis with trial sequential analysis of Randomized Controlled Trials

Ren, Y¹; Wei, M²; Liu, H³; Wang, Y⁴; Chen, H⁵; Shi, W⁶; Li, Z⁷; You, F⁸;

ABSTRACT

Rationale: The effect of dexmedetomidine as adjuvant of local anesthetic in wound infiltration is still uncertain. To assess the efficacy and safety of dexmedetomidine as an adjuvant to local wound infiltration anesthesia, we conducted this meta-analysis.

Search strategy: Based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Guidelines¹⁵ and the recommendations from the Cochrane Collaboration, a systematic search was performed on PubMed, Embase, the Cochrane Library and Chinese databases [Chinese National Knowledge Infrastructure (CNKI) and Wan-Fang database].

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 March 2020 and was last updated on 01 April 2020 (registration number INPLASY202040001).

infiltration; Comparison: Application of equal amount of normal saline as adjuvant of local anesthetics in wound infiltration; Outcome: The primary outcomes of this meta-analysis include: visual analogue scores (VAS, ranging from 0 to 10; 0 corresponding to no pain and 10 representing worst imaginable pain) at 1, 2,

4, 6, 8, 12, 24 and 48 hours postoperatively on resting state. The secondary outcomes of this article include: (1) the total rescue analgesic consumption in the 24-hour postoperative period; (2) time of first rescue analgesia within 24 hours after surgery; (3) rescue analgesia rate and rescue analgesia rate of different frequency. The adverse events include: Postoperative nausea (PON), Postoperative vomiting (POV), PONV, bradycardia, hypotension, respiratory depression, shivering, dizzy and wound infection; Study design: A Systematic Review and Meta-Analysis with trial sequential analysis of Randomized Controlled Trials.

Rationale: The effect of dexmedetomidine as adjuvant of local anesthetic in wound infiltration is still uncertain. To assess the efficacy and safety of dexmedetomidine as an adjuvant to local wound infiltration anesthesia, we conducted this meta-analysis.

Condition being studied: Acute wound pain is a nociceptive pain in the wound region of surgery, including peripheral sensitisation, secondary hyperalgesia, and spontaneous pain. It not only affects rapid rehabilitation but also reduces the perioperative quality of life and, therefore, has a negative effect on the patient's prognosis.² At present, the treatments for postoperative wound pain are mainly based on intravenous or oral opioids and non-steroidal antiinflammatory drugs (NSAIDs), such as fentanyl, morphine, and flurbiprofen. However, the use of opioids may cause a series of adverse reactions: postoperative nausea and vomiting (PONV), itching, respiratory depression, urinary retention. Dexmedetomidine (DEX) is a highly selective alpha 2-adrenergic receptor agonist, which has been used as an adjuvant in local anaesthetics. A few studies have shown that DEX could be used as an adjuvant for peripheral nerve block and spinal anaesthesia. A few studies have shown that dexmedetomidine could be used as an adjuvant for peripheral nerve block and spinal anaesthesia. Does dexmedetomidine provide a similar effect

on local wound infiltration? We wanted to see whether dexmedetomidine could improve analgesia when used in combination with local anaesthetics for wound infiltration. At the same time, we will further review the safety of dexmedetomidine in local wound infiltration.

METHODS

Participant or population: (1) Randomized controlled trials; (2) receive DEX as an adjuvant to local anesthetic in comparison with local anesthetic alone for local wound infiltration anesthesia.

Intervention: Dexmedetomidine as local anesthetic adjuvant for wound infiltration.

Comparator: Application of equal amount of normal saline as adjuvant of local anaesthetics in wound infiltration. Studies were excluded if they: (1) were abstracts, conference articles and protocols; (2) did not have complete data; (3) DEX was given intravenously in study.

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

Eligibility criteria: Studies were included if they met the following criteria: (1) RCTs; (2) receive DEX as an adjuvant to local anesthetic in comparison with local anesthetic alone for local wound infiltration anesthesia; (3) the study included DEX group and placebo (PLA) group, at least; (4) availability of full-text publication and there were no language restrictions. Studies were excluded if they: (1) were abstracts, conference articles and protocols; (2) did not have complete data; (3) DEX was given intravenously in study.

Information sources: Based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Guidelines and the recommendations from the Cochrane Collaboration, a systematic search was performed on PubMed, Embase, the Cochrane Library and Chinese databases [Chinese National Knowledge Infrastructure (CNKI) and Wan-Fang

database]. Additionally, Google Scholar was used to retrieve gray literature. The full search strategy is provided in the appendix. The retrieval time was from the time of database establishment to March 2020. A manual search was also performed for selecting articles and published reviews. Because the study is a meta-analysis, there is no need for ethical recognition and informed consent.

Main outcome(s): The following indexes were defined as primary outcomes: (1) rescue analgesia rate within 24 hours after surgery; (2) total rescue analgesic consumption in the 24-hour postoperative period; (3) incidence of DEX related adverse reactions: bradycardia and hypotension.

Additional outcome(s): The secondary outcomes of this article include: (1) visual analogue scores (VAS) at postoperatively on resting-state; (2) time of first rescue analgesia within 24 hours after surgery; (3) rescue analgesia rate of different frequency. Other adverse events include: postoperative nausea (PON), postoperative vomiting (POV), PONV, respiratory depression, shivering, dizzy, wound infection, sedation and urinary retention.

Data management: Data from the selected articles will be independently entered into an Excel spreadsheet by 2 reviewers (YFR and HL). The extracted information included the name of the main author, the year of publication, the type of surgery, the sample size, the dosage of DEX group and PLA group, and outcomes.

Quality assessment / Risk of bias analysis: The methodological quality of the included RCTs was reviewed by two reviewers (YFR and MLW) independently. The Cochrane Collaboration's risk of bias assessment tool was used. They evaluated the quality of each article from seven domains. If there were some disagreements, they discussed the disagreements to reach consensus or the issue was decided by two other reviewers (WS and HL). Finally, the low-bias, high-bias, and unclear judgments were obtained.

Search strategy: Based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Guidelines¹⁵ and the recommendations from the Cochrane Collaboration, a systematic search was performed on PubMed, Embase, the Cochrane Library and Chinese databases [Chinese National Knowledge Infrastructure (CNKI) and Wan-Fang database].

Strategy of data synthesis: Review Manager 5.3 was used for statistical analysis. Total rescue analgesic consumption and time of the first rescue analgesia were expressed by weight mean difference (WMD) and its 95% confidence interval (CI). Dichotomous outcomes were expressed by risk ratio (RR) and its 95% CI. The continuity correction was applied for zero event studies. P value <0.05 was considered statistically significant. VAS scores at different time after surgery are reported with 99% CI ($\alpha_{corrected}=0.01$) because a Bonferroni correction was applied.

Subgroup analysis: We performed subgroup analyses by the remaining pre-specified subgroup: time of incision infiltration (before skin incision versus before skin closure), type of local anesthetic (Ropivacaine versus Bupivacaine), DEX dose ($\leq 1.0\mu\text{g}/\text{kg}$ versus $>1.0\mu\text{g}/\text{kg}$), type of rescue analgesia (opioids versus non opioids), anesthesia mode (general anesthesia versus regional anesthesia) and type of incision infiltration (LWI versus CWI), et.al.

Sensibility analysis: Sensitivity analysis was conducted by excluding the study that the quality was rated as 'high risk'.

Language: English and Chinese.

Countries involved: China.

Keywords: Dexmedetomidine, adjuvant, wound infiltration, meta-analysis, trial sequential analysis.

Contributions of each author:

Author 1 - Conceptualized and designed the study, drafted the initial manuscript, participated in literature retrieval, collected data, carried out the initial analyses, reviewed and revised the manuscript;

Author 2 - Participated in literature retrieval, collected data, carried out the initial analyses, reviewed and revised the manuscript.

Author 3 - Conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Author 4 - Performed the literature searches and analyzed the data.

Author 5 - Performed the literature searches and analyzed the data.

Author 6 - Conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Author 7 - Performed the literature searches and obtained funding.

Author 8 - Performed the literature searches and obtained funding.