INPLASY PROTOCOL

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All authors declare no conflicts of interest.

Efficacy and Safety of Inhaled Methoxyflurane for Trauma Pain: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Review question / Objective: **To assess the efficacy and safety of inhaled methoxyflurane for trauma pain, including comparison with standard analgesia or placebo.**
Condition being studied: **Inhaled methoxyflurane in the management of acute trauma pain.**
Information sources: **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]. We also will further search the grey literature for other possible relevant studies, including Google Scholar, clinical trial databases, etc.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 November 2020 and was last updated on 27 November 2020 (registration number INPLASY2020110119).

INTRODUCTION

Review question / Objective: **To assess the efficacy and safety of inhaled methoxyflurane for trauma pain, including comparison with standard analgesia or placebo.**

Condition being studied: **Inhaled methoxyflurane in the management of acute trauma pain.**

METHODS

Participant or population: **Eligible patients were conscious adults aged ≥18 years**

presenting with trauma (fracture, dislocation, crushing, contusion, etc.) and requiring analgesia for moderate-to severe pain. Exclusion criteria included use of any other analgesic for the acute traumatic pain, contraindications to methoxyflurane administration in accordance with the summary of product characteristics17 (hypersensitivity to methoxyflurane or any fluorinated anesthetic; malignant hyperthermia; evidence of liver damage after previous methoxyflurane or halogenated hydrocarbon anesthetic use; clinically significant renal impairment; altered level of consciousness from any cause, including head injury; drugs or alcohol; clinically evident cardiovascular instability; or respiratory depression) or contraindications to any of the drugs included in the site's analgesic protocol, pregnancy, participation in another clinical trial within the previous 30 days, and medical conditions that could have affected the patient's ability to complete self-assessments of pain intensity.

Intervention: Experimental group: Inhaled methoxyflurane.

Comparator: Control group: placebo or standard analgesic treatment.

Study designs to be included: (1) Randomized controlled trials

Eligibility criteria: Exclusion criteria included use of any other analgesic for the acute traumatic pain, contraindications to methoxyflurane administration in accordance with the summary of product characteristics17 (hypersensitivity to methoxyflurane or any fluorinated anesthetic; malignant hyperthermia; evidence of liver damage after previous methoxyflurane or halogenated hydrocarbon anesthetic use; clinically significant renal impairment; altered level of consciousness from any cause, including head injury; drugs or alcohol; clinically evident cardiovascular instability; or respiratory depression) or contraindications to any of the drugs included in the site's analgesic protocol, pregnancy, participation in another clinical trial within the previous 30 days, and medical conditions that could have affected the patient's ability to complete self-assessments of pain intensity.

Information sources: 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]. We also will further search the grey literature for other possible relevant studies, including Google Scholar, clinical trial databases, etc.

Main outcome(s): Pain score at multiple timepoints were expressed by mean difference (MD) / standard mean difference (SMD) and its 95% confidence interval (CI). If the I^2 <50%, heterogeneity was considered not significant and the fixed-effects model was used; otherwise, we assumed that there was significant heterogeneity and used the random-effects model to calculate effect size. Furthermore, we performed the sensitivity analysis and subgroup analysis to explore the sources of heterogeneity. P value <0.05 was considered statistically significant.

Additional outcome(s): The time until pain relief, the use of rescue medication, use of the diluter hole during inhalation, assessment of medication performance (the satisfaction parameters included the judgment of patients on efficacy and investigators on practicality.), adverse events. The measurement data were expressed by mean difference (MD) / standard mean difference (SMD) and its 95% confidence interval (CI), as appropriate. The counting data were expressed by relative risk (RR) and its 95% confidence interval (CI). The I^2 statistics was used for assessing the studies' heterogeneity. If the I^2 <50%, heterogeneity was considered not significant and the fixed-effects model was used; otherwise, we assumed that there was significant heterogeneity and used the random-effects

model to calculate effect size. Furthermore, we performed the sensitivity analysis and subgroup analysis to explore the sources of heterogeneity. P value <0.05 was considered statistically significant.

Quality assessment / Risk of bias analysis: The methodological quality of the included RCTs were reviewed by two reviewers 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. Finally, the low-bias, high-bias, and unclear judgments were obtained. In order to obtain more information and ensure accurate quality assessment, if necessary, we will contact the author of the article by email or phone to elaborate on the methods they used in the research process. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used to assess the quality of evidence, which was classified as high, moderate, low or very low. Judgments included risk of bias, inconsistency, indirectness, imprecision and other considerations. GRADE Proversion 3.6 software, McMaster University, Hamilton, Ontario, Canada (http://gradepro.org/) was used.

Strategy of data synthesis: Review Manager 5.3 was used for statistical analysis. V The measurement data were expressed by mean difference (MD) / standard mean difference (SMD) and its 95% confidence interval (CI), as appropriate. The counting data were expressed by relative risk (RR) and its 95% confidence interval (CI). The I^2 statistics was used for assessing the studies' heterogeneity. If the I^2 <50%, heterogeneity was considered not significant and the fixed-effects model was used; otherwise, we assumed that there was significant heterogeneity and used the random-effects model to calculate effect size. Furthermore, we performed the sensitivity analysis and subgroup analysis to explore the sources of heterogeneity. P value <0.05 was considered statistically significant.

Subgroup analysis: We performed subgroup analyses by the remaining pre-specified subgroup: Different clinical groups (Inhaled methoxyflurane vs placebo / Inhaled methoxyflurane vs standard analgesic treatment), different types of surgery, dose of methoxyflurane, different ages, etc.

Sensibility analysis: Sensitivity analysis We will carry out sensitivity analyses by excluding studies classified as having a high risk of bias.

Language: None.

Country(ies) involved: China.

Keywords: Inhaled Methoxyflurane; Trauma Pain; Systematic Review; Meta-analysis.

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