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Review

Ketamine versus ketamine pluses atropine for pediatric sedation: A meta-analysis

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ABSTRACT

Objectives: The application of atropine for pediatric sedation in the emergency department remains controversial. Our objective was to perform a comprehensive review of the literature and assess the clinical indexes in groups with and without atropine use.

Methods: PubMed, EMBASE, and the Cochrane Library were searched for randomized and non-randomized studies that compared ketamine and ketamine plus atropine for pediatric sedation. The risk ratio with 95% confidence interval was calculated using either a fixed- or random-effects model according to the value of I^2.

Results: One retrospective study and four randomized controlled trials were identified to compare the clinical indexes. For the clinical indexes, the ketamine plus atropine group had better outcomes than the ketamine group in hypersalivation ($P < 0.05$), but indexes of rash and tachycardia were worse. The two methods of sedation were comparable for nausea, vomiting, desaturation, agitation and laryngospasm ($P > 0.05$).

Conclusions: Based on the current evidence, the group receiving atropine had reduced hypersalivation and increased rash and tachycardia; no differences were observed in nausea, vomiting, desaturation, agitation and laryngospasm between the two groups. Given that some of the studies were of low quality, additional high-quality randomized controlled trials should be conducted to further verify these findings.

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1. Introduction

As an important department of the hospital, the emergency department (ED) sees many patients daily, and children account for a large proportion of these patients. Children and adults feel similarly when they face trauma and pain. However, children are less able to adapt to the emergency environment than adults, which can lead to increased anxiety and pain [1]. What is more, when anxiety spreads among children and parents, the child's condition can worsen [2]. Procedural sedation and analgesia (PSA) is very important and can reduce unnecessary anxiety during the examination. At the same time, the selection of sedative drugs and, when multiple agents are used, drug interactions, can be challenging for emergency doctors.

Ketamine is a drug widely used for sedation and analgesia in emergency departments in many countries. It is a phencyclidine nonbarbiturate derivative, and its effects are achieved by combining sigma opioid receptors and *N*-methyl-D-aspartate [3]. Compared with other drugs, ketamine has the advantage of being fast acting with easy recovery. It exhibits excellent safety when used by non-anesthesiologists [4,5]. However, it has some side effects, including nausea, vomiting, agitation, transient rash, and hypersalivation [1,4,6]. Atropine is a well-known antimuscarinic drug [7] and is widely used to limit excessive mucosal secretions [8]. However, use of atropine delays the onset of saliva, which is itself a complication [9]. Therefore, whether atropine should be combined with ketamine to calm children is controversial, and many related experiments are being tested to investigate the problem [9,10]. Therefore, we collected articles about atropine use in ketamine sedation and conducted a meta-analysis to provide evidence to help guide the doctor's decision.

2. Methods

2.1. Search strategy

Two investigators reviewed the literature using the PICO principles, which include four elements: “P” refers to the patient, population or problem; “I” is the intervention; “C” stands for comparison; and “O” is

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the outcome. The key words ketamine, atropine, sedation and similar words were searched as [MESH] terms. The Boolean operators "AND" and "OR" were used to connect terms and search the literature in PubMed, EMBASE, and the Cochrane Library. The search was not limited to an initial time and language, but the deadline established was January 3, 2018. To avoid the omission of relevant documents, the researchers did not stipulate a patient population and selected the "All Fields" option rather than "Title/Abstract". In the rest of our work, type of population was limited by selection criteria. Based on the titles and abstracts, the researchers selected potentially eligible studies and read the full text of selected articles to assess eligibility. Disagreements between the two reviewers were decided by a third individual.

2.2. Selection criteria

(1) Participants: Patients aged <16 years old who were administered pediatric procedural sedation with ketamine in the emergency department were considered to meet the inclusion criteria. Patients over the age of 16 were excluded.
(2) Intervention and comparison: The group of patients who received ketamine with adjunctive atropine was the intervention group, and patients who received ketamine only or ketamine plus water or saline were placed in the control group. Patients who had received another drug for sedation were excluded.
(3) Outcomes: The clinical indexes, including vomiting, nausea, desaturation, hypersalivation, rash, tachycardia, agitation and muscle laryngospasm, were used as the outcomes.
(4) Study design: Randomized controlled trials and retrospective studies that compared ketamine with ketamine plus placebo were considered qualified.

2.3. Quality assessment

We used the Cochrane Handbook to evaluate the risk of randomized controlled trial data, and, according to the results, we classified the studies as high risk, low risk and unclear risk. In addition, for the retrospective study, we used the Newcastle-Ottawa Scale to evaluate the article quality, i.e., classify the trials into three levels of quality.

2.4. Data extraction

We extracted data on first author, publication date, country, study design, number of patients, mean age, percentage by sex, mean weight (kg), ASA scores and interventions. When disagreement occurred, the third reviewer made the final decision.

2.5. Data analysis and statistical methods

We used Review Manager version 5.3 to analyze the data. The risk ratio (RR) was calculated for the dichotomous outcomes. We used I^2 values to assess heterogeneity among the articles. If $I^2 > 50$, we used the random-effect model. If the opposite, we chose the fixed-effect model.

3. Results

3.1. Search results

A total of 545 articles were identified by our query method, of which 73 were from PubMed, 392 from EMBASE, and 80 from the Cochrane Library. Of these articles, 122 studies were eliminated as duplicates. Investigators selected 365 articles based on the meaning of the title and abstract. Finally, we chose five articles after considering the full text. The whole document screening process is reflected in Fig. 1.

3.2. Risk of bias assessment

In these included documents, the methodological quality of two types of experiments was evaluated according to their respective evaluation criteria. Only one the randomized controlled trials (RCTs) was low risk [11]; the rest were high risk. In the studies on RCTs that had low risk of reporting bias, only 3 [11-13] reported random sequence generation, and 3 [9,11,13] had a low risk for allocation concealment, binding of outcome assessment, and mention of participants and personnel in the text. For other biases, we were able to find clues in the texts. The only retrospective study was considered to be of good quality. Details about its contents are exhibited in Fig. 2a, b and Table 1.

3.3. Study characteristics

Of the 5 articles included, 4 studies were RCTs, and 1 article was a retrospective study. These articles described single-center studies, and nearly every article provided the general characteristics of the study population. In four articles, the patient's condition was evaluated by ASA; only one did not refer to an assessment of the patient's condition. Finally, 969 people were included in our study. Among them, 445 patients were sedated with ketamine, and 524 patients received ketamine plus atropine. The characteristics of these documents are presented in Table 2.

3.4. Outcomes of meta-analysis

3.4.1. Nausea

Two reports provided data (n = 340) on nausea. A fixed-effects model was used, and no significant heterogeneity was found ($I^2 = 0\%$, $P = 0.41$). The incidence of nausea in the ketamine + atropine group was not lower than that in the ketamine group (RR = 0.81, 95% CI: 0.45–1.46, P = 0.49). (Fig. 3)

3.4.2. Vomiting

There are five reports offering data (n = 954) on vomiting. Of them, 4 studies were randomized controlled trials and 1 study was a retrospective study. A fixed-effects model was used, and heterogeneity was slight ($I^2 = 11\%$, $P = 0.35$). Therefore, additional administration of atropine had no obvious inhibitory effect on vomiting after ketamine sedation (RR = 0.74, 95% CI: 0.53–1.03, P = 0.07). (Fig. 4)

3.4.3. Desaturation

Three reports reported the oxygen desaturation. We used a fixed model, and no significant heterogeneity was found ($I^2 = 0\%$, $P = 0.84$). The advantage of ketamine + atropine was not shown (RR = 0.92, 95% CI: 0.26–3.22, P = 0.90). (Fig. 5)

3.4.4. Hypersalivation

Three studies with 423 patients reported on the symptom of hypersalivation. A fixed model was used, and no significant heterogeneity was found ($I^2 = 0\%$, $P = 0.63$). The rate of hypersalivation that occurred in the ketamine + atropine group was lower than that in the ketamine group (RR = 0.37, 95% CI: 0.23–0.62, P = 0.0001) (Fig. 6).

3.4.5. Rash

The incidence of rash was provided in two reports. A fixed-effects model was used, and a small amount of heterogeneity was found ($I^2 = 19\%$, $P = 0.27$). The incidence of rash in the experimental group was higher than that in control group (RR = 2.44, 95% CI: 1.05–5.71, P = 0.04) (Fig. 7).

3.4.6. Tachycardia

Two articles with 340 patients reported the outcome of tachycardia. A fixed-effects model was used, and no significant heterogeneity was found ($I^2 = 0\%$, $P = 0.68$). The results showed that the tachycardia in

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