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The efficacy and safety of adrenergic alpha-antagonists in treatment of distal ureteral stones in pediatric patients: A systematic review and meta-analysis

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ABSTRACT

Objective: We carried out a systematic review and meta-analysis to evaluate the efficacy and safety of adrenergic alpha-antagonists as a medical expulsive therapy for ureteral stones in pediatric patients.
Methods: The PubMed, EMBASE and Cochrane Controlled Trials Register databases were searched up to January 2016. All randomized controlled trials and all cohort studies in which patients were randomized to receive either adrenergic alpha-antagonists or placebo for ureteral stones were identified. The outcome measures assessed were overall stone expulsion rate (primary), expulsion time (secondary), and treatment-emergent adverse events.
Results: Five trials with a total of 406 pediatric patients met the inclusion criteria. According to the doses of adrenergic alpha-antagonists, the pooling effects of adrenergic alpha-antagonists were analyzed, with a higher expulsion rate obtained than in controls, the stone expulsion rate (OR = 2.70, 95% CI 1.49 to 4.91, $P = 0.001$). Adrenergic alpha-antagonists statistically did not significantly decrease the number of the stone expulsion time with the placebo, the stone expulsion time (SMD = −4.65, 95% CI −9.76 to 0.45, $P = 0.07$). Safety assessments included common treatment-emergent adverse events (TEAEs) (OR = 2.01, 95% CI 0.74 to 5.48, $P = 0.17$). Compared with placebos, there was a higher stone expulsion rate with the adrenergic alpha-antagonists; in addition, fewer adverse effects were observed.
Conclusions: This meta-analysis may suggest that adrenergic alpha-antagonists are a safe and effective medical expulsive therapy choice for ureteral stones in pediatric patients. As the level of classification of evidence-based medicine, the level of evidence of our article is Ia. But it remains to need a large-scale multicenter randomized controlled study to be further confirmed.
Level of evidence: The level of evidence of our study is V.

Urolithiasis in children is a substantial public health problem. In the past few decades, the global incidence of urolithiasis in children has increased considerably [1]. In developed countries, the epidemiological data that showed urolithiasis in children, with a prevalence of between 1:1000 and 1:7600 in different parts of the USA [2], recently reported a five-fold increase in the incidence of pediatric urolithiasis over the last 20 years [3]. Noninvasive and minimally invasive surgical treatments for ureteral stones are now routine [4]; unfortunately, these procedures are invasive, have high costs and necessitate anesthesia in the pediatric population. If ureteral stones could be expelled with pharmacotherapy, procedures that necessitate anesthesia and their associated costs could possibly be avoided [5]. In recent years, there are several studies which have shown that alpha-antagonists can be used to augment spontaneous stone expulsion and reduce the time to expulsion of distal ureteral stones in adults [6–9]. Many recent studies about adrenergic alpha-antagonists in ureteral stones show a good effect [10–14]. Tamsulosin and doxazosin are two representative adrenergic alpha-antagonists in urolithiasis treatment. However, published data are limited regarding the use of alpha-blockers to manage distal ureteral stones in children.

The purpose of this study was to conduct a systematic review and meta-analysis of all available evidence from randomized controlled trials (RCTs) and cohort studies to assess the efficacy of adrenergic alpha-antagonists as a medical treatment for distal ureteral stones in pediatric patients.

1. Materials and methods

1.1. Inclusion criteria

Randomized controlled trials (RCTs) and multi-institutional cohort studies that met the following criteria were included: (1) a study design that included treatment with adrenergic alpha-antagonists; (2) the study provided accurate efficacy and safety data that could be analyzed, including the total number of subjects and the values of each index; (3) patients 2 to 18 y with DUS ≤10 mm; and (4) the full text of the study was accessible. If these inclusion criteria were not met, then the study was excluded from the analysis.

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1.2. Search strategy

MEDLINE (from 1966 to January 2016), EMBASE (from 1974 to January 2016), the Cochrane Central Register of Controlled Trials, and the reference lists of the retrieved studies were searched to identify RCTs and cohort studies that involved the effects of adrenergic alpha-antagonists treatment. The following search terms were used: adrenergic alpha-antagonists, distal ureteral stones, pediatric, randomized controlled trials and cohort study.

1.3. Trial selection

When the same study was published in various journals or in different years, the most frequently cited one was used for the meta-analysis. If the same group of researchers studied a group of subjects in multiple studies, then each study was included. Two reviewers independently selected the articles for inclusion by assessing the eligibility of full papers against the review inclusion criteria. Disagreements were resolved by discussion, if necessary, with a third reviewer. A flow diagram of the study selection process is presented in Fig. 1.

1.4. Quality assessment

The methodological quality of each RCT was assessed in terms of the means of patient allocation to various arms of the study, allocation concealment, blinding, and loss to follow-up. Also, the methodological quality of cohort study was assessed in terms of the means of patient allocation to various arms of the study, exposure variable and covariates, sample size calculation and propensity score matching. Patients were then classified qualitatively according to the guidelines published in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [15]. Based on the quality assessment criteria, the quality of each study was broadly classified as one of the following three categories: A, all quality criteria were met (adequate), and the study was deemed to have a low risk of bias; B, one or more of the quality criteria were only partially met (unclear), and the study was deemed to have a moderate risk of bias (Table 2). Differences were resolved by discussion among the reviewers.

1.5. Data extraction

The following information was collected: (1) the name of the first author and the publication year; (2) the study design and sample size; (3) the therapy that the patients received; (4) the source of the patients; and (5) data including expulsion time, stone expulsion rate, and side effects.

1.6. Statistical analysis

The meta-analysis was carried out using Review Manager 5.1.0 [15], if data were sufficiently similar. The funnel plot was referred to in this meta-analysis and did not provide evidence of publication bias. Results would be expressed as odds ratios (ORs) for dichotomous outcomes, and continuous outcomes include mean difference (MD) or the standardized mean difference (SMD), both with 95% confidence intervals (CIs). The standard mean difference was used if the outcome data were not recorded in a congress method. A "fixed-effect" was used if there was no significant heterogeneity; otherwise, a "random-effects" statistical model was used. Tests for heterogeneity were performed using I^2 statistic with the level of significance set at $P < 0.05$. The presence of publication bias was evaluated using a funnel plot. The trials of lowest quality were excluded.

2. Results

2.1. Characteristics of individual studies

Four RCTs and one cohort study [5,16–19] were included in the analysis; 225 studies were excluded from the meta-analysis because they were not suitable for the study. The characteristics of the individual studies are listed in Table 1, and the trial selection process is presented in detail in Fig. 1. The trials included in the analysis were conducted in 3 different countries, located in Asia, Africa and America. The analyzed

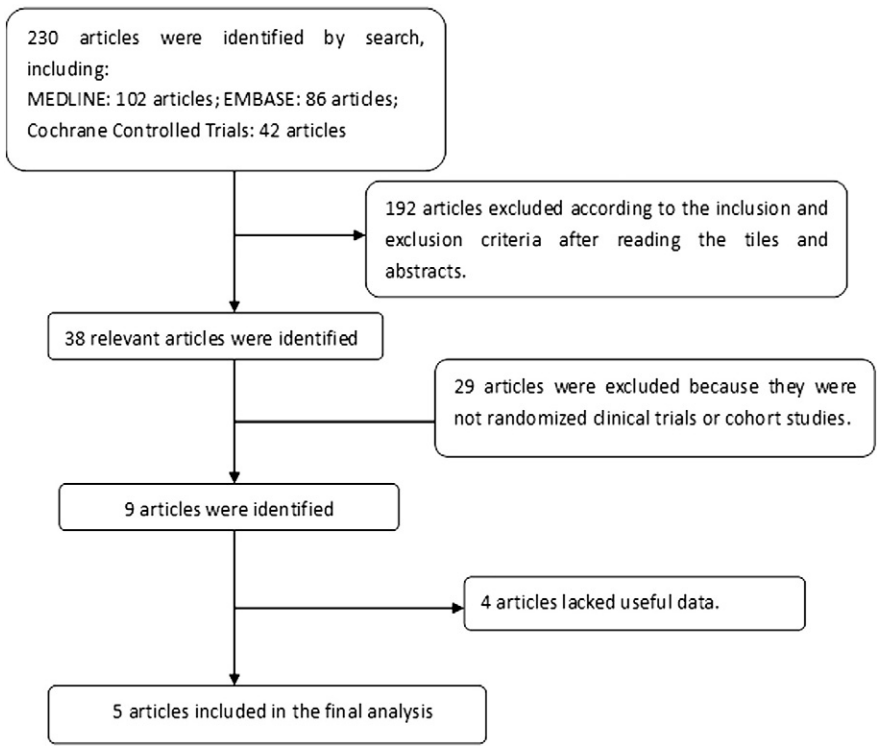

Fig. 1. The flow diagram of the study selection.