Journal of Pediatric Urology (2015) 11, 321–327

Review article

Medical expulsive therapy for pediatric urolithiasis: Systematic review and meta-analysis

Nermarie Velázquez [1], Daniel Zapata [1], Hsin-Hsiao S. Wang, John S. Wiener, Michael E. Lipkin, Jonathan C. Routh

Division of Urologic Surgery, Duke University Medical Center, Durham, NC, USA

Correspondence to: J.C. Routh, Division of Urologic Surgery, Duke University Medical Center, DUMC 3831, Durham, NC 27710, USA, Tel.: +1 919 684 6994; fax: +1 919 681 5507

Jonathan.Routh@duke.edu (J.C. Routh)

Keywords
Pediatric; Kidney stone; Urolithiasis; Nephrolithiasis; Review; Systematic; Meta-analysis

Received 16 December 2014
Accepted 3 April 2015
Available online 27 June 2015

Summary

Objective
Kidney stone disease has become more common among children and young adults. Despite its well-documented success in adults, published success rates of medical expulsive therapy (MET) for pediatric urolithiasis vary widely. Our objective was to determine whether the aggregated evidence supports the use of MET in children.

Methods
We searched the Cochrane Controlled Trials Register, clinicaltrials.gov, MEDLINE, and EMBASE databases, and recently presented meeting abstracts for reports in any language. In addition, the bibliographies of included studies were then hand-searched. The protocol was prospectively registered at PROSPERO (CRD42013005960). Inclusion criteria were children (aged $\leq$ 18 years) with urolithiasis treated with medications with the specific goal of increasing spontaneous stone passage rate, including but not limited to alpha-adrenergic blockers (e.g., tamsulosin or doxazosin), calcium channel blockers (e.g., nifedipine), or other adjuvant medications (e.g., steroids or tolterodine). Manuscripts were then assessed and data abstracted in duplicate, with differences resolved by the senior author. Risk of bias was assessed using standardized instruments. Descriptive statistical analyses were performed as appropriate.

Results
We identified 11,197 studies, five of which (3 randomized controlled trials, 2 retrospective cohorts) were included in the pooled meta-analysis. Although we found little evidence of significant publication bias, we were unable to assess the likelihood of other forms of bias (allocation, selection) for most included studies due to reporting limitations. The pooled results demonstrate that MET significantly increased the odds of spontaneous stone passage (OR 2.21, 95% CI 1.40–3.49). Between-study heterogeneity was not statistically significant (I^2 = 14%, p = 0.36). Bivariate meta-regression models revealed no significant association between the likelihood of stone passage and study COI (p = 0.9), study country (p = 0.7), patient age (p = 0.4), patient gender (p = 0.4), duration of follow-up (p = 0.3), or stone size (p = 0.7). Side effects of MET were reported to be minimal. Relatively few patients reported any adverse effects at all; the most commonly reported issue was somnolence. Concerns about biases affecting the published outcomes of the included studies exist due to the low quality of the randomized controlled trials reviewed for analysis. However, there was little visual evidence of publication bias noted on the funnel plot, as confirmed by the Begg test (p = 0.5).

Conclusions
Consistent with the adult literature, pediatric studies demonstrate that treatment with MET results in increased odds of spontaneous ureteral stone passage and a low rate of adverse events. Although the accumulated literature is limited by inconsistent and/or incomplete reporting, there is nonetheless a clear, cumulative positive effect of MET on stone passage among children. The available evidence thus supports a prominent role for MET in treatment algorithms for pediatric urolithiasis.

[1] Both authors contributed equally to this paper.

http://dx.doi.org/10.1016/j.jpurol.2015.04.036

Introduction

Kidney stone disease is becoming increasingly common among children and young adults [1,2]. Children who develop kidney stones are likely to have recurrent stones, and as such they are at high risk for undergoing multiple stone removal procedures over the course of their lives. Published data would seem to indicate that most children with urolithiasis are treated conservatively with observation to allow spontaneous stone passage, although there is significant inter-institutional variation in surgical treatment rates [3].

In adults, medical expulsive therapy (MET) has been shown to be successful at increasing spontaneous stone passage rates and at reducing the number of stone-related surgical procedures [4,5]. MET typically involves taking a daily medication, usually an alpha-adrenergic antagonist such as doxazosin or tamsulosin, to dilate the distal ureter and promote the spontaneous passage of the stone. In a large meta-analysis in adults, MET was found to increase the chances of spontaneous stone passage by 65% (pooled risk ratio 1.65, 95% CI 1.45—1.88) [4]. Whether MET is similarly effective for children, given their relatively smaller ureters, is less clear; few studies have assessed the efficacy of MET in the treatment of urolithiasis in children. The results of these studies are inconsistent and limited by the variation in study designs, patient selection, and outcome measures. Conflicting results have even been reported among the published randomized controlled trials (RCTs) of MET [6—8].

In light of these differences, the goal of this systematic review is to evaluate the accumulated literature on the medical management of pediatric urolithiasis.

Patients and methods

Search strategy

We searched the Cochrane Controlled Trials Register, clinicaltrials.gov, MEDLINE, and EMBASE electronic databases for studies published between January 1990 and October 2013 in any language based upon PRISMA guidelines [9]. This date range was chosen to provide a contemporary selection of studies. We used the exploded search terms: "urolithiasis", "nephrolithiasis", "kidney stone", or "stone". These were then restricted to articles retrieved under a second search for the exploded search terms "pediatric", "child", or "children".

Reference lists of included studies were manually screened for any additional studies. We also manually searched for unpublished abstracts presented at relevant scientific meetings: American Urological Association, Society for Pediatric Urology, American Academy of Pediatrics Section on Urology, Pediatric Academic Societies, World Congress of Endourology, Société Internationale d'Urologie, and the European Association of Urology. The protocol was prospectively registered at PROSPERO (CRD42013005960).

Selection criteria

Inclusion criteria were children (aged $\leq$ 18 years) with urolithiasis treated with medications with the specific goal of increasing spontaneous stone passage rate, including but not limited to alpha-adrenergic blockers (e.g., tamsulosin or doxazosin), calcium channel blockers (e.g., nifedipine), or other adjuvant medications (e.g., steroids or tolterodine). These patients were then compared against children with urolithiasis undergoing no treatment or other non-MET drug therapy (e.g., non-steroidal anti-inflammatory drug [NSAID]).

Our goal was to include only RCTs; however, we a priori decided that if few pediatric RCTs met inclusion criteria, we would also include observational studies, provided that data from a comparison group was reported. RCT and cohort studies were analyzed as subsets and reported separately. Inclusion criteria included report of the number of patients treated and the fraction for which the treatment was successful. No manuscript was excluded based on method of analysis, definition of success, language of publication, or perceived quality/susceptibility to bias. In cases of ambiguity or where study reporting made evaluation difficult, we attempted to err on the side of inclusiveness.

Data abstraction

Two reviewers (N.V. and D.Z.) independently reviewed all study abstracts in duplicate with disagreements resolved by the senior author (J.C.R.). Full text articles appearing to meet selection criteria were reviewed, and study data was abstracted in the same manner. Manuscripts published in languages other than English were translated by study authors fluent in that language and/or by institutional translation staff. Abstracted data included patient-level factors (patient age, stone size, stone passage rate, time to passage, MET agent, adverse events) and study-level factors (study design, country of origin, conflict of interest disclosure, funding). COI was identified by disclosure publication. Our primary outcome was spontaneous stone passage.

Risk of bias assessment

Bias assessment was undertaken using the Cochrane Collaboration checklist. Funnel plots were visually assessed for evidence of publication bias. Bias assessment did not influence the planned meta-analysis.

Statistical methods

Descriptive statistical analyses were performed as appropriate. For univariate pooling, standard Dersimonian—Laird random-effects models were constructed [10]. Study heterogeneity was assessed using the Higgins—Thompson method [11]. Given the small number of eligible studies, meta-regression was not performed.

Influence analyses were performed by sequentially removing individual studies and thus verifying that the effect estimates had not significantly changed. No significant differences with inclusion/exclusion of any study were noted.

All statistical analyses were performed using STATA/SE version 11.0 (College Station, TX, USA) and RevMan version