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The Evidence Paradox of the Effectiveness between the Paediatric and Adult Stone-Forming Population: A Narrative Review

Key Words

Pediatric population · Medical expulsive treatment · α-Blocker/alfuzosin/tamsulosin/doxazosin

Abstract

Aim/Objective: To identify trends in the evidence base regarding the effectiveness of using α-blockers in children versus adults and compare outcomes. ***Methods:*** A literature search up using the key words including urolithiasis/renal/ureteric stone in children/paediatric population, medical expulsive treatment (MET), α-blocker/alfuzosin/tamsulosin/doxazosin. Included were randomized or controlled clinical trials in paediatric stone formers (aged ≤18 years). Outcome measures for assessment included the overall stone expulsion rate, expulsion time, the number of pain episodes and adverse drug effects and/or reactions. Further comparison of efficacy levels using respective studies from the adult population was performed in order to identify trends, similarities and differences. ***Results:*** A total of 8,259 articles were identified. Full text evaluation was possible for 28 articles. Although the picture is clearer in the paediatric group, the lack of reproducible results in adults certainly poses serious questions about data collection, analysis and interpretation in each individual study. The apparent paradox is due to the methodological differences between studies. ***Conclusion:*** The effectiveness of α-blockers and other medication as MET needs to be studied in multi-institutional, double-blind, placebo-controlled studies that would aim to prove superiority to placebo in contemporary clinical situations, with realistic end points and standardized outcome measure determination.

Introduction

Urinary stone disease in children is uncommon. From historic data, it is evident that the prevalence is considered to be 2–3%. In endemic countries, like Turkey and Pakistan, it may reach up to 15% of the paediatric population [1, 2]. In developed countries, a reported rise in incidence is probably due to improvements and increased use of diagnostic procedures as well as changes in dietary habits over the past decades [3]. There is lack of contemporary evidence from properly designed epidemiologic studies. In a most recent study by Tasian and Copelovitch [4], the incidence of nephrolithiasis in children has increased during the last 25 years by approximately 6–10% annually and is now 50 per 100,000 adolescents. On the

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contrary, stone management in children has changed significantly with the introduction of metabolic profiling and shockwave lithotripsy as well as endourologic surgery [5]. There are many similarities between the management of the adult and paediatric patient groups.

The use of α-blockers to facilitate the passage of ureteric calculi or residual fragments has been widely studied in adults, yet in children despite the availability of relatively few data, the level of evidence appears to be stronger. In this review, we critically appraise the literature regarding the efficacy and safety of α-blockers as medical expulsive treatment (MET) of urinary stones in children and compare the evidence base with that obtained from the adult population.

Materials and Methods

We performed a literature search in the electronic databases PubMed, Embase, Medscape, and the Cochrane Library according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement up to December 2015 using the key words: urolithiasis/renal/ureteric stone in children/paediatric population, MET, α-blocker/alfuzosin/tamsulosin/doxazosin. Additional evidence was collected by identifying studies from the respective references of selected articles. Inclusion criteria were prospective and retrospective trials in which α-blockers were investigated following the acute colic episode or intervention in the paediatric population of stone formers (aged ≤18 years). Reviews and expert opinion articles were also appraised but were not considered in the conclusions. The risk of bias of individual studies is reflected by the level of evidence, which corresponds to the study design and interpretation of data. To further strengthen the evidence for the safety profile of the drug in question, we included studies for the use of α-blockers in neurogenic urinary tract dysfunction in children, which were also analysed using the PRISMA principles. Outcome measures for assessment included the overall stone expulsion rate, expulsion time, number of pain episodes and adverse drug effects and/or reactions. Further comparison of efficacy with the adult population was performed in order to identify trends, similarities and differences. Due to the plethora of evidence in adult nephrolithiasis, the most recent and highest quality evidence studies were selected.

Results

For the paediatric population, a total of 8,259 articles were identified from the databases by using the key words in combinations. Further selection according to title relevance yielded 32 articles that included most of the key words in the title and abstract and could provide evidence for the end points in question. Full text evaluation of these articles was sought and was possible for 28 articles (87.5%). A quality assessment and classification according to the level of evidence followed. In more detail, 11 articles actually dealt with the effects of α-blockers on ureteric stones in the paediatric population. Two meta-analyses of randomized studies were identified (level of evidence, LE: 1a) [6, 7], 4 prospective randomized studies (LE: 1b) [8–11], one well-designed cohort study (LE: 2b) [12], one systematic literature review (LE: 3) [4] and 3 expert panel reports (LE: 4) [13–15]. Three articles that discussed the metabolic evaluation and medical treatment of paediatric nephrolithiasis were identified and they consisted 2 well-designed cohort studies (LE: 2b) [16, 17] and one expert panel report (LE: 4) [18].

Finally, 14 articles addressed the safety and efficacy of α-blockers in children with neurogenic lower urinary tract symptoms and neuropathic bladder. Four were prospective randomized studies (LE: 1b) [19–22], 6 studies were well-designed prospective cohorts without randomization (LE: 2a) [23–28], 2 studies were retrospective (LE: 2b) [29, 30], while one review (LE: 3) [31] and one expert panel report (LE: 4) [32] were also found. For the adult population, 5 articles were chosen that represent the latest and highest quality of published evidence to provide for arguments in the discussion [33–37], including the most recent meta-analysis and the only double-blind, placebo-controlled randomized study (LE: 1a and 1b, respectively) to date. A flow diagram of the results is shown on Figure 1 and LEs are explained in Table 1.

Efficacy of MET in Children

The 2 meta-analyses identified comprise the latest and more reliable evidence regarding the usefulness of stone expulsive management in children. The studies were published consecutively and have its origin from different investigator/institutional groups and maintain high methodological standards. In the first study by Glina et al. [7], 3 randomized controlled studies up to October 2014 are included and it is concluded that the use of α-1 adrenergic antagonists increases the overall probability of stone expulsion by 27%, with refined odds rising to 33% for calculi <5 mm and 34% >5 mm (LE: 1a). The second meta-analysis by Velázquez et al. [6] includes the aforementioned controlled trials as well as 2 retrospective cohorts for data pooling. The results were again in favour of MET, as significantly increased odds of spontaneous stone passage were demonstrated (OR 2.21, 95% CI 1.40–3.49). More importantly, the second meta-analysis excluded the variability of study type, country, stone size, follow-up duration and gender as factors that would affect the favourable expulsion rates; however, a point was made for

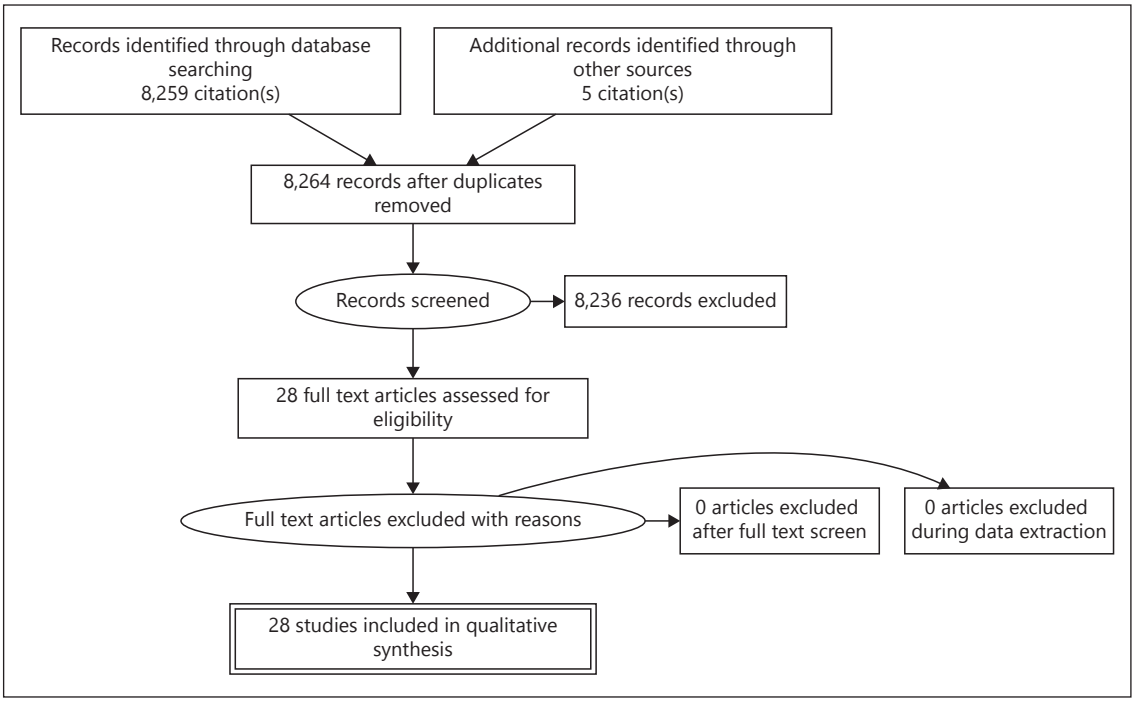

Fig. 1. PRISMA flowchart of selected studies.

Table 1. Levels of evidence-based studies [38]

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomized trials
1b	Evidence obtained from at least one randomized trial
2a	Evidence obtained from one well-designed controlled study without randomization
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

the heterogeneity and relative poor quality of the randomization methods (LE: 1a).

In the study by Mokhless et al. [8], a statistically significant difference in mean stone expulsion time in favour of tamsulosin was recorded (8.2 vs. 14.5 days) for a follow-up of 4 weeks prior to definitive treatment by interventional means (LE: 1b). Similar results were reported in the study by Aldaqadossi et al. [11], again in favour of tamsulosin for an equal follow-up period (7.7 vs. 18 days) (LE: 1b). Erturhan et al. [10] studied prospectively doxazosin in distal ureteric stones and found expulsion rates of 70.8 vs. 28.5% in the control group of ibuprofen for a follow-up of 3 weeks (LE: 1b). Similar results were reported by Aydogdu et al. [9] for equal follow-up periods (84 vs. 70%), although the authors concluded the contrary despite calculating statistical significance (LE: 1b). Nevertheless, the retrospective case-matched cohort by Tasian et al. [12] with 6 weeks follow-up failed to demonstrate any statistically significant difference between the tamsulosin and the analgesic groups. It was only when the

analysis was adjusted for stone size and location that tamsulosin was associated with better spontaneous passage, notably with a wide confidence interval (OR 3.31, 95% CI 1.49–7.34) (LE: 2b). Of the remaining articles, the majority favour MET, with the exception of the review by Atan and Balcı [13] who support that in the face of limited comprehensive studies, calculi <10 mm should either be allowed to pass spontaneously or treated aggressively when symptomatic (LE: 4).

Safety of MET in Children

In general, the safety profile of α-blockers as MET was reported as satisfactory. Velázquez et al. [6] commented that side effects of MET were minimal, with only few patients complaining of somnolence during treatment. In the systematic review by Glina et al. [7], there is no mention of side-effects analysis. When examining the prospective series individually, no adverse effects were reported, other than somnolence, nausea and vomiting experienced by one patient in the study conducted by Erturhan et al. [10] and 3 patients experiencing mild nasal congestion in the study by Aldaqadossi et al. [11]. No adverse reactions to tamsulosin were observed in the retrospective cohort by Tasian et al. [12]. Nevertheless, in the literature concerning the neurogenic lower urinary tract dysfunction and symptoms, more conclusive arguments can be found regarding the safety of α-blocker administration in children. In the phase IIb/III dose-ranging, double-blind controlled trial by Homsy et al. [19] a 5.8% frequency of side effects for tamsulosin was reported against 4.9% for placebo. The authors concluded that further studies are possible due to the favourable safety profile of tamsulosin in children with neuropathic bladder (LE: 1b). A similarly favourable side-effect profile is reported by Yucel et al. [21] in their study of tamsulosin vs. biofeedback for dysfunctional voiding and urinary retention, with no drug-related side effects reported in the α-blocker group, while Kramer et al. [20] did not report any side-effect results in their study (LE: 1b). All the prospective trials (LE: 2a) as well as the retrospective cohorts (LE: 2b) reported no minimal adverse effects, with the most notable reports being those observed by Yang et al. [27] of negligible decreases of systolic and diastolic blood pressure and that of Austin et al. [23] with one patient developing mild postural hypotension, which resolved with dose reduction (doxazosin 0.5 mg). In their population pharmacokinetic study, Tsuda et al. [28] demonstrated for the first time that α-blocker exposure (tamsulosin) in paediatric patients was comparable to that in healthy adults when weight-based dose administration was implemented. In the aforementioned studies, most researchers used either doxazosin 0.5–2 mg or tamsulosin 0.2–0.8 mg with no evidence of weight-dependent dose calibration.

Discussion

The introduction of MET either as a primary (to aid spontaneous passage) or an adjuvant (post shockwave lithotripsy) modality in adults has helped in a better understanding of the natural history of ureteric calculi at the very least. When assessed individually, the multitude of evidence in the literature leaves little room to doubts regarding the efficacy and safety of MET. In their Cochrane Collaborative Systematic review of the role of α-blockers in MET, Campschroer et al. [33] make a clear recommendation in favour of α-blockers due to a higher stone-free rate and a shorter time to stone expulsion while reporting only few and minimal adverse effects (LE: 1a). However, several and considerable biases are also reported, such as double-blind studies comprising only a quarter of the data pool, reporting of incomplete data, wide variation among studied variables between studies and high withdrawal rates. Certainly all the above compromise on evidence quality. The multicentre, placebo-controlled randomized study by Pickard et al. [34] published in the high impact-factor journal *Lancet* is considered by many to be the single best quality evidence-based study that demonstrates the non-superiority of a blocker over placebo in primary MET (LE: 1b). Indeed, the investigators use impeccable and clearly explained methodology to reach the conclusion that neither tamsulosin nor nifedipine proved superior to placebo in averting further management in the form of active intervention due to failed clearance after 4 weeks. As with all studies, it is not without weaknesses, especially regarding the definition of relevant end points and the respective use of the results obtained. Nevertheless, the quality of the trial raises the stakes and prompts for more in-depth and quality analysis with further research. The latest published meta-analysis (LE: 1a) on adjuvant MET by Skolarikos et al. [35] again favours the use of pharmacological agents, including α-blockers, for residual fragments after shockwave lithotripsy.

The relevant literature for the paediatric population appears more clear and definitive. The meta-analysis by Velázquez et al. [6] supports the integration of α-blockers in the treatment algorithms for paediatric urolithiasis despite concerns regarding inconsistencies similar to the studies in adults. The same recommendation is made by

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the majority of all the good-quality studies that we reviewed. Furthermore, a low rate of adverse events is quoted and this class of medication is generally deemed safe for administration in children. However, there was more robust evidence identified in studies of children with lower urinary tract neurogenic dysfunction than studies involving ureteral stones and the quality of reporting was also better in the former trials. By comparison, the studies in the paediatric population of stone formers appear to be more consistent in terms of better defining end points and reporting outcomes than the comparable studies of the adult population. The need for more high-quality research is highlighted by most authors in the concluding sections for both age groups. Another very interesting observation is that in the latest publications regarding the optimization of shockwave lithotripsy outcome both in adults and children, there is no mention of the use of α-blockers as adjuvant treatment despite the existing evidence. One plausible explanation would be the increasing complexity and difficulty in analyzing and interpreting the outcomes correctly if yet another, and more complex, parameter was introduced. Nevertheless, it feels rather counterintuitive not to study a factor that has been used off license by most urological practices globally for at least the past decade and which is constantly scrutinized.

It is evident that the scientific community has not yet reached a consensus regarding the place of α-blockers in the management of urinary stones, although this appears to be less so in paediatric nephrolithiasis, where primary and adjuvant MET seems to be established as standard treatments. Some comments can be made for this evidence paradox and disparity among otherwise good-quality research from renowned institutions. A straightforward argument can be made for the broad range of methodological parameters and end points used to support the same hypothesis, that is, α-blockers aiding in the expulsion of ureteric stones. On the other hand, the same variation in investigation parameters that achieves a statistically significant difference may substantiate the validity of the hypothesis even more. Although the standardization of prospective randomized trials through the adherence to dedicated and strict protocols is widely accepted and practiced, the literature shows that results and biases are reported and substantiated in only a handful of studies to a full, thus compromising evidence quality. While it is very difficult to have absolute control over all individual study parameters and explain complex statistics in simple meaningful words, specific and clear individual end points can be sought for and outlined by careful methodological planning and structured reporting.

Conclusion

It is clear that the race is far from over and that more focused and standardized research is required in order to draw meaningful conclusions with real-time clinical applications. Although the picture is clearer in the paediatric stone-forming population, the lack of reproducibility in adults certainly poses serious questions about data collection, analysis and interpretation in each individual study. The effectiveness of α-blockers and other medication as MET needs to be studied in multi-institutional, double-blind, placebo-controlled studies that would aim to prove superiority to placebo in contemporary clinical situations, with realistic end points and standardized outcome measure determination. A more comprehensive and flexible strategy could therefore be formulated for more timely and efficient ureteric stone clearance in both adults and children with urolithiasis.

So it may be that the apparent paradox existing between the evidence for the efficacy of MET between adult and paediatric age groups may be due to methodological differences between the studies that have been performed. However, one further hypothesis may be of relevance. It might be that α-blockers work better on ureteric propulsion kinetics in children than in adults perhaps related to hitherto unknown differences in ureteric smooth muscle pharmacodynamics and receptor responsiveness in children. This hypothesis is, of course, difficult to explore but might nevertheless be a hitherto unconsidered factor of the paradox.

Disclosure Statement

The authors declare no conflict of interest.

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