Medical expulsive treatment in pediatric urolithiasis

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ABSTRACT

The frequency of stone disease in childhood ranges between 0.1-5 percent. Stone disease occurs as a result of environmental, metabolic, anatomical, infectious and nutritional factors. Percutaneous nephrolithotomy, ureteroscopy, laparoscopic surgery, open surgery and extracorporeal shock wave lithotripsy are treatment alternatives for stone disease during childhood. However, these methods are not completely innocent. Some complications may occur after these procedures. These procedures are generally not cost-effective. Even invasive procedures have high success rates, so medical expulsive treatment modalities have become an alternative for a group of patients. Nonsteroidal anti-inflammatory drugs, antimuscarinic drugs, phosphodiesterase type 5 inhibitors, steroids, calcium channel blockers and alpha blockers are treatment alternatives used for this modality in the literature. The drug is chosen according to the location, size, and composition of the stone, recent technology, cost, surgeon's experience and surgeon's and the parents' preferences. In this review article the following topics will be discussed such as "Why medical expulsive treatment is needed during childhood? Which drug should be chosen for which stone type? How long should a treatment of urolithiasis last?"

Keywords: Pediatric, stone, treatment

Introduction

Stone disease in children develops in association with metabolic, anatomical, infectious, and nutritional factors. The incidence of stone disease in children ranges between 0.1, and 5 percent.^[1] All ages of the childhood, and both genders can be affected equally. In this review article we will describe why medical expulsive treatment (MET) is necessary in children, and which drugs should be used for which types of stones, and for how long. Urinary system stone disease in children is managed with open surgery, extracorporeal shock wave lithotripsy (ESWL), laparoscopic or robot-assisted uretero-pyelolithotomy, percutaneous nephrolithotomy (PCNL) (mini, microperc), rigid and/or flexible ureteroscopy (URS) and MET. Choice of the treatment for a specific patient is determined based on the location, size, composition of the stone, urinary system anatomy, available technology, cost of the treatment, experience of the physician, and preference of both the physician, and the patient's relative.^[2]

Invasive treatments require expertise, and technical material. Though interventional treatment

is successful up to 100%^[3,4] they are not completely free of complications. Complications related to URS range between 10-20 percent. A 3-5% of them constitute major complications (perforation, avulsion, and ureteral stricture). ESWL-related complications (15-32%) include perirenal collection of fluid, and subcapsular hematoma etc, and retreatment rates after ESWL range between 4, and 50 percent.^[5] Besides URS, and ESWL are costly procedures.^[2,6] Therefore despite very high success rates of invasive treatments, MET should be thought for a specific group of patients. As cited in the literature many drugs have been tried for MET. These drugs include nonsteroidal anti-inflammatory drugs (NSAIDs), antimuscarinic drugs, phosphodiesterase type-5 inhibitors (PDEIs-5), steroids, calcium channel blockers, and alpha-blocker agents.^[7-10] However in clinical trials, alpha-blockers, and calcium channel blockers have been found to be more effective, and successful rather than other drugs. Mechanism of action of these 2 drug groups involves prevention of uncoordinated contractions induced by the stone without eliminating peristaltic activity of the ureter. This phenomenon reflects on clinical practice

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as passage of increased number of stones within a short time with lower doses of analgesics.^[11]

Literature information

In their series of a total of 90 patients in the tamsulosin, and follow-up groups with distal ureteral stones measuring 5-10 mm in diameter, Sayed et al.^[12] reported rates of stone expulsion (88.9 vs. 51.1%), time elapsed till stone passage (7.32 vs 12.53 days) as indicated in parentheses. Diclofenac was more frequently used in the follow-up group, and the authors did not report any side effect of the drug therapy. Porpiglia et al.^[13] performed a study on 96 patients (nifedipine group, n=48, and deflazacort group, n=48) with stones ≤ 1 cm, and indicated that drug treatments increased stone expulsion rate (35 vs. 79%), shortened time to stone passage (7 vs. 20 days), and decreased the need for analgesics (15 mg vs. 105 mg) when compared with the follow-up group in addition to reliability of the drug therapy. In another study by Porpiglia et al.^[14] performed on 86 patients with lower ureteral stones with a diameter of 3.5-10 mm, any difference between drug groups (nifedipine 30 mg + deflazacort 10 mg, and tamsulosin 0.4 mg + deflazacort 10 mg treatment groups) and follow-up group was not detected as for stone expulsion rates (80 vs. 85%), and time to stone passage (9.3 vs. 7.7 days).

According to the 2007 Guideline of American Urological Association, and 2013 Guideline of European Association of Urology, relative superiority of alpha-blockers has been indicated. According to 2013 Guideline of European Association of Urology, all alpha-blockers have similar effects. Outcomes of experimental studies of MET in children started to be published after demonstration of effectiveness, safety, and reliability of MET in adults. Experimental studies related to doxazosin use in various diseases in the pediatric age group have been already performed.^[15-17] Use of tamsulosin in pediatric age group was approved by FDA in 2013.^[18]

Location, and size of the stone are important parameters for the success of medical expulsive treatment. Ureteral stones constitute 20% of all cases with urinary system stone disease. Seventy percent of ureteral stones are localised in the distal ureter.^[19] MET should be targeted to these stones. Studies performed in adults have demonstrated spontaneous passage of 39-98% of ureteral stones smaller than 4 mm, while only 25-53 % of stones of ≥ 5 mm in diameter could pass spontaneously.^[20-23] Stones larger than 10 mm had no chance of spontaneous passage.^[24] In the light of available data, in adults, suitability of MET for ureteral stones with a diameter of 5-10 mm has been indicated.^[7,9] However in the pediatric age group, reports have stated that stones smaller than 3 mm can pass spontaneously, while stones of ≥ 4 mm require treatment.^[25,26] In children with distal ureteral stones measuring 4-10 mm in diameter MET appears be an appropriate treatment.

Clear-cut information about the use of medical expulsive treatment in children is lacking. However when data related to studies performed in adults were taken into consideration, in the 2013 Guideline of European Association of Urology, duration of MET in adults was limited to maximum 30 days.^[27]

In 4 clinical trials MET was used in the management of pediatric stone disease. In the first study which included 39 children with radio-opaque lower ureteral stones ranging between 2-10 mm in diameter, the patients were divided into only ibuprofen, and ibuprofen + doxazosin (0.03 mg/kg) groups. Treatment lasted for 3 weeks. In the first group children with a mean age of 5.1 years and stone diameter of 5.8 mm were treated. While the second group included patients with a mean age of 6.2 years and mean stone diameter of 7.1 mm. Stone expulsion rates were 70, and 84% in Groups 1, and 2, respectively without any statistically significant intergroup difference. Although the authors indicated that doxazosin was not superior over analgesic treatment in the distal ureteral stones smaller than 10 mm, they also stated that these relevant studies should be repeated using different doxazosin doses in the treatment of patients with bigger stones.^[28] The second study included 61 children with radio-opaque distal ureteral stones smaller than 12 mm. The first arm of the study (n=33; mean age, 7.3 years; mean stone size, 8.2 mm) received a standard analgesic (ibuprofen) + tamsulosin, and the second arm (n=28; mean age 7.1 years; mean stone size, 7.8 mm) was treated with a standard analgesic (ibuprofen) + placebo. Tamsulosin dose was adjusted to the age of the patients (>4 years, 0.4 mg, and <4 years 0.2 mg). Treatment lasted for 4 weeks. Success rates of MET were 87.8% in Group 1, and 64.2% in Group 2. Though for stones smaller than 5 mm rates of effectiveness of MT did not differ, for stones measuring 5-10 mm, success rates were 84.6, and 53.8% in Groups 1, and 2 respectively. In this study tamsulosin was found to be beneficial in the expulsion of distal ureteral stones with diameters ranging between 5, and 10 mm.^[29] The third study included 50 children (mean age, 6.6 years) with radio-opaque distal ureteral stones. Group 1 received ibuprofen + placebo, and Group 2, ibuprofen + doxazosin (0.03 mg/kg) for a period of 3 weeks. Mean size of the stones, and stone expulsion rates were 4, 45 mm, and 28.6% in Group1, and 4.58 mm, and 70.8% in Group 2, respectively. In addition to higher rates of stone passage, number of painful episodes, and need for analgesic decreased.^[30] A total of 449 children were included in the last study. Treatment lasted for 6 weeks. Ninety-nine patients with stones smaller than 10 mm who completed the study received daily 0.4 mg doses of tamsulosin, while the other 99 patients received only an analgesic. Any difference between groups as for age, gender, body weight, location, and size of the stone was not detected. Stone expulsion rates in the tamsulosin, and analgesic groups were 55, and 44%, respectively. ($p=0.03$).^[31] In all of these studies, history of ureteral, and/or bladder surgery, presence of anatomic

Table 1. Publications on medical expulsive treatment in children

Author	Medical expulsive treatment	Number of Patients (n)	Stone size (mm)	Location of the stone	Follow-up period	Stone passage rate
Aydoğdu ^[28]	Doxazosin	19	<10 mm	Distal ureter	3 weeks	84%
	Ibuprofen	20				70%
Mokhless ^[29]	Ibuprofen + tamsulosin	33	<12 mm	Distal ureter	4 weeks	87.8%
	Ibuprofen + placebo	28				64.2%
Erturhan ^[30]	Ibuprofen + doxazosin	24	<10 mm	Distal ureter	3 weeks	70.8%
	Ibuprofen + placebo	21				28.5%
Tasian ^[31]	Tamsulosin	99	<10 mm	All	6 weeks	55%
	Analgesic	99				44%

urinary system anomalies, vesicoureteral reflux, neurogenic/non-neurogenic voiding dysfunction, bilateral or nonopaque ureteral stones, serious hydronephrosis, attacks of renal colicky pain, and use of diuretic and/or calcium channel blockers were exclusion criteria of the study. In a recent review article on pediatric stone disease, use of MET was investigated. The authors indicated that high-quality randomized studies were not available yet, and effectiveness of doxazosin on stone expulsion was not very well established (Table 1).^[32]

In children MET is primarily used for the expulsion of residual stone fragments retained within lower one-third of the ureter after ESWL rather than primary lower ureteral stones. Indeed in the management of pediatric stone disease, ESWL is used frequently, and stones are left to spontaneous passage after ESWL. Addition of alpha blockers to treatment will be helpful in the expulsion of these stones within a relatively short time with lesser pain. In studies performed in adults varying results have been achieved. In some studies beneficial outcomes have been attained, while in others expected benefits could not be gained.^[33-37] However in the pediatric age group inadequate data are available on this issue. Therefore, clinical trials aiming at clarification of the role of MET in the expulsion of residual stones fragmented by ESWL rather than primary lower ureteral stones should be planned.

In conclusion, 2013 Guidelines of European Association of Urology indicated that inadequate data are available about use of MET in children.^[27] In the light of the limited data with alpha-blocker treatment 4-10 mm stones located within distal ureter can be passed. Comprehensive studies which will yield more precise data should be conducted aiming at investigation of effectiveness of MET in the expulsion of both primary stones, and also residual upper ureteral stone fragments after ESWL.

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