Phytotherapy as ancillary treatment after urinary stone lithotripsy in pediatric age



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AIM: Small stone fragments (NSRF) may be observed after mini-invasive lithotripsy. A 3-components herbal extract drug was tested in young patients presenting NSRF to assess efficacy, safety and tolerability.

MATERIAL AND METHODS: Patients aged 6-18 years, treated by endo-urological procedures in 5-year period, were randomly divided in 2 groups. Group A received a 3-components phytotherapic composed of Herniaria hirsuta and Peumus boldus plus water oral intake for 12 days/month in 3 months. Group B had no adjuvant phytotherapy. Group A and B were divided in 2 subgroups, according to persistence of NSRF. Patients were evaluated after the endo-urological procedure (Time 0), at 3-months therapy (Time 1) and after 3-months follow-up (Time 2). Persistence or development of new micro-lithiasis, adverse effects and urological check were registered.

RESULTS: Thirty-four patients were enrolled (Group A=15, Group B=19). Two patients were excluded. In Group A, 6 patients were stone free at Time 0 and had no recurrence, while 7 patients (53.8%) had NSRF at Time 0, reduced to 3 (23.0%) and to 2 (15.4%) at Time 1 and 2 respectively. In Group B, 11 patients (57.9%) presented NSRF at Time 0, reduced to 8 (42.1%) and 7 (36.8%) at Time 1 and 2. The difference was significant (Time 1 p=0.006, Time 2 p=0.009). No adverse effects were reported.

DISCUSSION AND CONCLUSIONS: The drug was effective in preventing new stones development and reducing significantly stone fragments persisting after endo-urological lithotripsy in children, with optimal tolerability and no adverse effects.

KEY WORDS: Arbutin, Boldine, Phytotherapy, Pediatrics, Umbelliferone, Urinary tract stones

Introduction

Urinary tract stones are not uncommon in pediatric age patients. In western countries, renal and ureteral calculi are mostly found in the pyelo-calyceal and ureteral system, whereas bladder stones are observed more commonly in bowel augmented bladders, in not emptying bladders or in chronically infected lower urinary tract ^{1,2}. Prevalence of pyelo-calyceal and ureteral stones is apparently increasing in the last few decades in developed countries, whereas lower urinary tract stones are still more frequent in developing countries ³. A better ultrasonographic diagnostic technology and a more spread use of ultrasonography in pediatric population could be responsible for the increasing number of diagnosis of urinary tract stones observed nowadays in the developed countries. Moreover, dietary factors (as malnutrition or hyperproteic diet), poor water intake, metabolic abnormalities and environmental changes, have been postulated as influencing the urinary stone development in children growing in different socio-economic situations ^{4,5}. Pediatric urolithiasis is estimated as 1% of overall stone disease of adults ⁴.

Urological treatment of lower and upper urinary tract stones has been quickly evolving in the last two decades in children ⁶. Innovative mini-invasive treatments, most-

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ly extracorporeal and endourological procedures, have been progressively proposed and adopted also in very young children and infants ^{2,3} extracorporeal shock waves lithotripsy (ESWL): rigid, semi-rigid and flexible ureterolithotripsy (ULT), retrograde intrarenal surgery (RIRS), mini-percutaneous lithotripsy (Mini-PCNL) and last but not least, micro-percutaneous lithotripsy (Micro-Perc) and are now offered to pediatric patients presenting urinary stone disease ⁶⁻⁷. The progressive miniaturization of the endourological instrumentation and a continuous development of new technologies allow Pediatric Urologists to avoid open surgery in almost 100% of pyelo-calyceal and ureteral stones in pediatric age ⁸.

As a consequence of stones fragmentation by endoscopic ballistic or laser energy or by extracorporeal shock waves, lithotripsy may not achieve a complete clearance as not significant residual fragments (NSRF) may often remain inside the urinary tract. NSRF are considered as small pieces of the original stone (2 to 5 mm in diameter) and are reported as occurring in the 10-30% of the lithotripsy treatments both in adult and pediatric age ^{9,10}. NSRF are usually asymptomatic and may be eliminated spontaneously after lithotripsy, but may cause colicky pain and urinary tract infections (UTI). Moreover, it may be responsible for stone recurrence at short and long term follow-up.

Complete clearance of NSRF from urinary tract is a significant goal of stone disease treatment, especially in pediatric patients. Recently, a new drug obtained by a combination of extracts from three different medicinal plants, has been proposed to reduce the risk of persistent NSRF after stones endo-urological fragmentation and of correlated UTI.

Aim of this study is to evaluate the efficacy and safety of this new medical herbal drug in a cohort of pediatric patients treated by endourologic procedures for upper tract stone disease.

Materials and Methods

The study design was performed as a prospective, randomized, two-way crossover trial in pediatric age patients who underwent endourologic procedures for upper tract urinary stones. The study protocol was approved by the Institutional Ethical Committee of our Pediatric Hospital. Patients treated by endourologic procedures (ULT, RIRS, Mini-PCNL or Mini-perc) for pyelocalyceal stones were progressively recruited in a specific database. Inclusion criteria were: age between 6 and 18 years; upper tract stones treated by endourologic lithotripsy; normal renal function. Exclusion criteria were: age under than 6 years or over 18 years; vesical stones; open surgery for stone removal; concomitant major clinical problems as severe neuro-psychological damage chronic renal failure suspected or confirmed allergy to one of the drug's chemical components. All

patients were evaluated immediately after lithotripsy (Time 0) by renal and urinary tract ultrasound (US), plain X-ray of kidneys and ureters (X-ray), urine colture, blood laboratory tests including creatinine blood test, electrolytes (sodium, potassium, calcium magnesium), differential blood count, transaminase (gamma-glutamyltransferase and alanin-amino-tranferase), total protein, alkaline phosphatase, prothrombine time (PT), partial thromboplastine time (PTT). The same exams were repeated at the end of the study, according with the procedure. A specific informed consent was obtained by the parents.

Patients were randomly divided in 2 groups, according with the offered treatment:

- Group A) received oral phytotherapy with a threecomponents herbal extract (Renalit-combi provided by Bio-Stilogit Pharmaceuticals) composed of *Herniaria hirsuta* (mother tincture, 40 mg), Uva ursi (dry herb, 300 mg - titrated at 60 mg of Arbutin) and Peumus boldus (dry herb, 200 mg - titrated at 0,1 mg of Boldine), plus standard hydropinic therapy with a high volume of water intake (50 ml/kg/day) with frequent bladder emptying.

- Group B) was treated only with the standard hydropinic therapy for a 3-months period after lithotripsy.

Group A and B patients were further divided in 2 subgroups, according with the persistence or not of residual stone fragments after endourologic lithotripsy. All Group A patients received the 3-components phytotherapy after lithotripsy, independently from the presence or not of minimal residual stone fragments. No other pharmacological treatments were adopted in both groups, except in case of breakdown symptomatic colicky pain or UTI episodes.

After 3 months from the study admission (Time 1), patients repeated the urological evaluation, including US, X-ray and blood laboratory tests with urinalysis. At the end of the study (6 months from the study entry – Time 2), patients were evaluated by urological interview, US and urinalysis. Follow-up was completed by monthly telephone calls with regular questioning.

The following data were recorded on the database at Time 1 and 2:

– urological evaluation, UTI, colicky pain episodes, microscopic or macroscopic haematuria;

- NSRF persistence or clearing, stone recurrence by US or X-ray or CT scan if needed;

- Any adverse event, spontaneously reported by the patients or parents.

For statistical analysis of the results, Chi-square test and Student-T test were adopted when appropriate.

Results

From January 2011 to December 2015, a total number of 108 patients were observed and treated for symp-

tomatic upper tract urinary stones at the Division of Pediatric Urology of the "Bambino Gesù" Children's Hospital. An overall number of 144 procedures were performed, including 36 ESWL, 70 retrograde endoscopic procedures (ULT and RIRS) and 36 percutaneous lithotripsies (Mini-PCNL and Micro-Perc). Among this population, 34 pediatric patients were progressively enrolled on the present study, as they were full fitting the inclusion criteria, and randomized in 2 groups, according with the different therapeutic approach. Group A included 15 patients, Group B 19 patients. Two patients of group A, stone free after endo-urological procedures, failed to complete the phytotherapeutic protocol and were drop out.

Finally, the patients included in the study were:

- Group A: 13 patients, aged from 6.5 to 18 years (median age 11.6 years), who received adjuvant phytotherapy;

- Group B: 19 patients, aged from 6.2 to 17.9 years (median age 12.5 years), without any pharmacological treatment.

The two groups were similar for age, urological treatment and NSRF distribution (p=not significant). The results regarding the 2 groups are shown on (Fig. 1). The data on distribution of the results, according with the different modalities of endourologic treatment, are summarized in (Table I).

NSRF were found at Time 0 in 53.8% of Group A patients and in 57.9% of Group B (p=not significant.). At Time 1 and 2, the difference between the two Groups was significant (Table I). At Time 1, NSRF were present in 23.0% of Group A and in 42.1% of Group B patients (p=0.009).

At Time 3 NSRF were observed in 15.4% and in 36.8% of Groups A and B respectively (p=0.006). The distribution of the minor stones residuals (NSRF) after the different modalities of endo-urological treatment (RIRS/ULT, Micro-perc, Mini-PCNL) are shown in (Table I), with the results of the phytotherapeutic treatment at Time 1 and 2.

One case of new stone was observed at Time 2 (6 months from endo-urological lithotripsy) in a 15 yearold female patient of Group B presenting cystinuria type 1. No new urinary calculi were recognized in the Group A patients at 6 months follow-up (Time 2). No increase of number or size of the residual stone fragments was recognized in patients of Group A. In 2 cases of Group B patients, a limited increase of stone residuals was observed at Time 2 (from 3 to 4 mm and from 3 to 5 mm of the maximum diameter).

No side effects were reported by patients and their parents and no adverse effects were observed by urological interview and periodic evaluation, during the pharmacological treatment. Blood pressure check was never modified during the phytotherapeutic approach.

Discussion

The urological treatment of upper urinary tract stones is still a challenging issue in pediatric age patients, although urinary calculi are almost uncommon, representing only 1% of lithiasis in adult patients ⁴. New technologies aimed to a more efficacious lithotripsy have been recently developed, as high energy laser or ultrasound sources and new endo-urologic instrumentations have been introduced in the last two decades. The progressive miniaturization allows, nowadays, the use of these tools in very young children with body weight under 10 kg. High quality scopes are offered with very reduced calibre access, as we have in Mini-PCNL (from 22 to12 Fr calibre) or in Micro-perc (4.85 Fr calibre of the metallic needle) for a mini-invasive percutaneous access ^{7,10}. Very thin semirigid or flexible ureteroscopes (8.5-7.5 Fr calibre) are available with reduced calibre, ureteral sheets and endourologic accessories usable for retrograde access to the high urinary tract also in children ^{6,12}.

The risk of stone recurrence in pediatric urinary lithiasis is higher than in adult patients ^{2,13}. Several reasons have been suggested: higher incidence of metabolic and genetic causes of the lithiasis as cystinuria and hyperossaluria, frequent association with urinary tract congenital abnormalities as hydronephrosis, megaureter or vesico-ureteral reflux, reduced calibre of the urinary tract ^{1,3}. Moreover, the advent of miniaturized endourologic procedures for lithotripsy and the diffuse use of ESWL have increased, in our opinion, the possibility to have stone residuals in the urinary tract more frequently than open surgery stone removal 6. Often, the residual fragments after extracorporeal or endourologic lithotripsy are considered not clinically significant if presenting a diameter of less than 5 mm and absence of symptoms (NSRF) 9,10,13. All these stone residuals can be expelled through the urinary tract with no or minimal inconvenience for the patient also in pediatric age, due to the good compliance of the urinary tract walls. Nevertheless, a significant risk of ureteral colicky pain episodes are observed during the spilling attempts. Moreover, they may cause UTI episodes and stone recurrence at short or long term, especially if any concomitant lithogenetic factor is present, as metabolic, genetic or related to a congenital abnormality of the urinary tract. All these factors are more frequent in paediatric age stone disease ^{2,6}.

The experience shows that it is not easy to remove, using endoscopic basket, forceps, laser-tripsy or other endoscopic techniques, all the residual stone fragments that can persist both after endourologic procedures or extracorporeal lithotripsy. NSRF have been found in 58% of patients in our study, more frequently after RIRS procedures (77%).

The use of herbal extracts to treat UTI and urinary stones is not new, as empirically adopted for several centuries in North Africa population (especially in Morocco) with excellent tolerability ¹⁴. A number of plants with therapeutic effects have been used by traditional medicine: *Herniaria hirsuta, Herniaria glabra, Amni visnaga, Zea mays, Opuntia ficus india, Peumus boldus, Phyllanthus niruri* are some of the herbs used as medicinal drugs ^{14,15}. A new pharmacological herbal drug has been used in our study, composed of a combination of active principles derived from three plant extracts, specifically designed for the treatment and prevention of recurrence of urinary lithiasis and its consequences:

- Arbutin: 60 mg/dose titred from *Uva ursi* (300 mg in 10 ml syrup), with anti-inflammatory and anti-bacterial actions ¹⁵⁻¹⁷.

– Umbelliferone, from *Herniaria hirsuta* (40 mg/day in 10 ml syrup), that acts as anti-cristalloid aggregation and reduces bacterial adhesivity on the pyelo-calyceal and ureteral urothelium^{18,19}.

– Boldine, 100 $\mu g/dose$ titred from *Boldo* (200 mg in a capsule, at night), with diuretic and pro-cynetic actions on renal and ureteral structures 20 .

This treatment, associated with high volume water intake, was administered to the Group A patients in 12 days per month (12 consecutive days), during a 3-months period. In children younger than 7 years, the dose was reduced by 50%. No adverse effects were registered and no significant screening laboratory test modifications were observed at the end of treatment (Time 1) and at the end of the 3-months follow up (Time 2). No episodes of abdominal pain or ureteral colicks pain were reported by the patients.

The drug (Renalit-combi provided by Bio-Stilogit Pharmaceuticals srl, Bagno a Ripoli, Florence, Italy) has shown anti-inflammatory and anti-adhesive properties on the upper tract urothelium, with a pro-cynetic activity on the pyelo-ureteral musculature, gently promoting ureteral peristalsis. The 3-components vegetal drug has been proposed positively for the treatment and the prevention of urinary micro-lithiasis. Specifically, *Uva ursi* extracts are well known to act against inflammatory reac-

tions of the urinary tract ¹⁴ and are currently used for UTI episodes treatment and risk of recurrence 16,17. Herniaria hirsuta extracts, containing Umbelliferone, have been demonstrated to reduce calcium oxalate crystallization in vitro ^{18,21} and in vivo in experimental models 19, further reducing the adhesivity of cristalloids on the urothelium. Boldine is the substance extracted from Boldus peumus, a Mediterranean herb that should have procynetic and diuretic action on kidneys and ureters, stimulating the peristalsis of urinary tract musculature for an active stones elimination ²⁰. The action mechanism on the urinary tract of these three-components is not well known. The herbal extracts are referred to act reducing the adhesivity of cristalloids and of bacteria on the urothelial layer and stimulating ureteral contractions and peristalsis to promote the expulsion of stone fragments or of small diameter stones from the urinary tract ¹⁷. Moreover, the crystallization of calcium oxalate and cystine is inhibited ^{14,18,19}. No experience has been provided till now on the use of the 3-components herbal extract drug (Renalit-combi) on paediatric and adolescent patients treated by endo-urological procedures for upper tract urinary stones. In the present study, we demonstrated that the incidence of residual fragments was significantly lower in the group of children who received prophylactic use of Renalit-combi after endourological stone fragmentation and persisting micro-lithiasis. The stone fragments decreased from 53.8% to 23.0% at the end of pharmaceutical therapy, further reduced to 15.4% at 3-months follow-up (Table I). The obtained results demonstrate that the positive effect of the 3-components herbal drug was continuous during the 3-months follow-up, with further progressive reduction of residual micro-lithiasis from Time 1 to Time 2 (Table I). No side effects, UTIs or significant pain episodes were reported during the phyto-therapeutic treatment and after the 3-months follow-up. No recurrent lithiasis was observed in the stone-free Group A patients who received the herbal drug as prophylactic treatment.

TABLE I - Summary of treatr	nents in Group A a	end B, according to th	he endourological treatment
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NSRF in Group A and B patients according to the endourological treatment

Group	Treatment	0	0					
		Total Patients	Time 0		Time 1		Time 2	
			Patients	%	Patients	%	Patients	%
A R M M T	RIRS/ULT	6	4	66.6	2	33.3	1	16.06
	Micro-Perc	3	1	33.3	1	33.3	1	33.3
	MINI-PCNL	4	2	50.0	1	25.0	0	0
	Total	13	7	53.8	3	23.0	2	15.4
В	RIRS/ULT	9	7	77.7	5	55.5	5	55.5
	Micro-Perc	4	1	25.0	1	25.0	1	25.0
	MINI-PCNL	6	3	50.0	2	33.3	1	16.6*
	Total	19	11	57.9	8	42.1	7	36.8

*1 newly developed stone (cystine)



Fig. 1: Patients aged 6-18 years treated by endourological procedures for upper tract urinary stones with (Group A) and without (Group B) phytotherapy.

In a recent systemic review on 16 randomized controlled trials, Authors concluded that herbal medicines were in general effective to induce stone size reduction and clearance, significantly better than placebo ²². Moreover, herbal remedies were in general devoid of side effects. Citrate treatment seems to be more effective than phytotherapy in decreasing the size of existing urinary calculi and in decreasing the urinary excretion rate of uric acid ²¹. Nevertheless, citrate have appeared to induce gastroin-testinal disturbance in a fraction of patients, while herbal medicine treatments have shown no adverse effects.

In conclusion, point of weakness of the present study may be that the results are coming from a single centre experience on an innovative and not standardized treatment.

The drug dosage was empirically determined. The number of enrolled patients was limited and the randomization was not blind. The strength of the study is based on the homogeneity of the 2 groups of enrolled patients for age, stones dimensions and endo-urological treatment. Moreover, to our knowledge, this is the first study on the use of phytotherapy as ancillary treatment for preventing recurrent stones after endoscopic of upper tract lithotripsy. Finally, we demonstrated the high efficacy of the treatment with a 3-components herbal extracts drug to reduce significantly the number of residual microlithiasis after endo-urological lithotripsy. No adverse effects, UTIs or pain episodes were observed during the treatment and the follow-up.

Although further randomized controlled trials are welcomed, the originality of the study is focused on the demonstrated significant efficacy and high tolerability of the proposed phytotherapeutic approach, which has been tested on a group of patients in pediatric and pubertal age.

Conclusion

Phytotherapy may be considered as complementary therapy for paediatric patients after urinary stone lithotripsy. No side effects were reported by patients and their parents, but further studies, with wider population, should be conducted.

Riassunto

SCOPO DELLO STUDIO: Calcolosi renale di modesta entità si può osservare in alcuni pazienti sottoposti a litotrissia mini-invasiva. Lo scopo dello studio è valutare l'efficacia, la sicurezza e la tollerabilità di un estratto di base vegetale in questi pazienti.

MATERIALI E METODI: Pazienti di età compresa tra 6 e

18 anni, trattati per via endoscopica per calcolosi renale, sono stati divisi in 2 gruppi: il gruppo A ha ricevuto un integratore composto da Herniaria hirsuta e Peumus boldus per 12 giorni al mese per 3 mesi; il gruppo B non ha assunto alcuna terapia adiuvante. Nei pazienti veniva, quindi, valutata la persistenza di calcolosi renale immediatamente dopo la procedura endo-urologica (Tempo 0), dopo 3 mesi di terapia (Tempo 1) e dopo 3 mesi di follow-up (Tempo 2). Venivano riportati, quindi, persistenza o sviluppo di microlitiasi ed eventuali effetti collaterali.

RISULTATI: Trentaquattro pazienti sono stati arruolati (15 per il Gruppo A e 19 per il Gruppo B); due pazienti sono stati esclusi. Nel gruppo A, 6 (46.2%) pazienti erano liberi da microlitiasi al Tempo 0 e non hanno mostrato recidive, mentre 7 pazienti (53.8%) ne mostravano al Tempo 0, ridotti a 3 (23%) e 2 (15.4%) rispettivamente al Tempo 1 e 2.

Nel gruppo B, 11 pazienti (57.9%) mostrava microlitiasi al Tempo 0, ridotto a 8 (42.1%) e 7 (36.8%) rispettivamente al Tempo 1 e 2. La differenza tra i due gruppi è statisticamente significative (Tempo 1 p=0.006; Tempo 2 p=0.009). Non è stato riportato alcun evento avverso.

DISCUSSIONE E CONCLUSIONE: La fitoterapia si dimostra un ausilio efficace nel ridurre il rischio di sviluppo di microlitiasi dopo litotrissia endoscopica in età pediatrica, con buona tollerabilità e nessun effetto collaterale.

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