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Efficacy of a fixed combination of *Centaurii herba*, *Levistici radix* and *Rosmarini folium* in urinary lithiasis

Results of an open randomised cohort study

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Efficacy of a fixed combination of *Centaurii herba*, *Levistici radix* and *Rosmarini folium* in urinary lithiasis

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Urolithiasis is a common disease and plays an important role in urological practice. It describes the formation of urinary calculi in the urinary system. Undetected in most cases, patients take however notice of calculi if they obstruct the urinary tract thereby inducing spastic pain attacks.

The pathophysiology of urolithiasis is still under debate and seems to be multifactorial such as physicochemical and metabolic trigger mechanisms. A main physicochemical trigger is supersaturation, e.g. as expressed as the ratio of urinary calcium oxalate or calcium phosphate concentration to the solubility, which is the driving force for stone formation. About 80% of stones are composed of calcium oxalate with variable amounts of calcium phosphate. Calcium oxalate supersaturation is independent of urine pH, but calcium phosphate super-

saturation increases rapidly as urine pH rises from 6 to 7. Other triggers are of metabolic nature, such as imbalances between excretions of calcium, oxalate, and water which create supersaturation.

Control of urine pH

Hypercalciuria, most common metabolic abnormality in calcium stone formers, is most often familial and idiopathic; it is strongly influenced by diet. The link between the urine pH and the type of lithiasis is well known, therefore a control of urine pH is required. In healthy individuals urinary pH ranges between 4.6 and 7.5, depending on dietary habits (amount of ingested animal proteins and vegetables) (2, 6, 13, 18, 29).

Noticeable, the incidence of urolithiasis is variable with respect to geographical dis-

tribution. Reno-ureteral calculosis, typical in elder patients with mainly calcium oxalate and phosphate (70% of all renal stones) is currently more frequent in economically developed countries. The prevalence rate is between 4% and 20% varying considerably with respect to environmental factors (17, 24, 27). In Europe, approximately 5% of the population suffers from urinary tract diseases, the prevalence of urolithiasis in this population is 30%, more often in men than in women (5, 26, 27, 29).

Most of the calculi are discharged spontaneously

A peculiarity of urinary lithiasis is the presence of small, non-obstructive reno-ureteral calculi. A high percentage of reno-ureteral calculi is eliminated spontaneously (4, 9, 11, 22). Treatment includes the increase of urinary flow along with prevention of relapses and urinary infections (16, 19, 21). Conservative treatment of reno-ureteral lithiasis is always indicated, if the calculi do not interfere with urinary passage or cause hydronephrotic changes, and in the absence of pyelonephritis (17).

SUMMARY

Urolithiasis describes the formation of calculi in kidney and efferent urinary passages. If these calculi jam urinary passages, it is often associated with typical spastic pain attacks. Certain herbal drugs play a special role in urolithiasis prophylaxis and treatment. The herbal medical product Canephron® N, a combination of *Centaurii herba*, *Levistici radix* and *Rosmarini folium*, is established in the therapy of urolithiasis, the indication is proven by some clinical studies. In a randomised open monocentric add-on cohort study, the efficacy of Canephron® N was investigated for the treatment of urolithiasis. The herbal medical product was administered in 135 patients additionally to standard therapy, for comparison 102 patients were treated with standard therapy only. Canephron® N favours the spontaneous elimination of small calculi and significantly decreases leucocyturia, especially associated with urinary infection. Therefore it is justified to suggest the combination for prevention and/or in addition to standard therapy of urolithiasis.

Key words

Urolithiasis, herbal therapy, *Centaurium* spp., *Levisticum officinale*, *Rosmarinus officinalis*, open randomised cohort study, efficacy

Herbal Therapy

Herbal drugs play a specific role in the conservative treatment of urologic complaints, especially for secondary prevention of urinary tract infections and renal inflammation as well as for the prevention of renal gravel. In cases of urolithiasis herbal drugs as e.g. *Equiseti herba*, *Levistici radix*, *Urticae herba/folium* and *Solidaginis herba* are used since many centuries. The main therapeutic strategy is the increase of urinary flow and the dilution of the urine, resulting in a re-

duction of stone formation. The clinical efficacy is mainly due to several additive or synergistic pharmacodynamic effects. Herbal drugs for therapy of urolithiasis were shown to be safe during long-term therapy (2, 18). Scientific monographs of the herbal urologicals are available from the ESCOP (European Scientific Cooperative on Phytotherapy; monographs from 2003 and 2009). For some drugs and preparations the traditional use in urology has been acknowledged by the European Committee on Herbal Medicinal Products (hitherto in monographs on *Equiseti herba*, *Urticae herba* and *folium*, and *Solidaginis herba*).

Canephron® N is a fixed combination of centaury herb (*Centaureum spec.*), lovage root (*Levisticum officinale* Koch) and rosemary leaves (*Rosmarinus officinalis* L.). Overall, the drugs exert diuretic (12, 31), spasmolytic (1, 30), anti-inflammatory (10, 20, 28), antimicrobial (7, 8, 14, 15), and nephroprotective effects (23). In Moldova the combination is registered as diuretic for single or additive treatment of chronic infections of urinary tract, for non-infectious chronic inflammations of the kidneys and for urolithiasis. The combination had been introduced to the market in several countries more than 40 years ago. Some trials had shown its efficacy in the treatment of urinary tract diseases alongside with an excellent safety profile (2, 13, 18).

The present cohort study was initiated to gain further data on the effectiveness of the herbal combination in the treatment of urolithiasis as a supportive therapeutic option in addition to standard therapy.

Materials and methods

Study design and study centre

The clinical study was performed as a randomised open mono-centre add-on cohort study at the Urology and Surgical Nephrol-

ogy Clinic of the State Medical and Pharmaceutical University (SMPU) »Nicolae Testemițanu«, Chisinau, Republic of Moldova. The study was approved by the local ethics committee.

Patients

Inclusion criteria were in-patients with reno-urethelial stones up to 0.7 cm of diameter; patients with severe disruption of the urinary passage and acute obstructive pyelonephritis were excluded. A detailed diagnosis including anamnestic data and documentation of previous and concomitant medication was made before enrolment into the study.

Intervention

The patients were randomly allocated to the herbal combination additionally to standard medication (study group) or to standard medication only (common anti-inflammatory, analgesic or spasmolytic treatment; control group) at hospitalisation. One coated tablet of the study medication Canephron® N contains powdered *Centaurei herba* (18 mg), *Levistici radix* (18 mg), and *Rosmarini folium* (18 mg) as active ingredients. In the study group the patients were advised to take 2 tablets 3 times daily in accordance with product information. Randomisation was performed by random digit tables with stratification of the parameter »stone location«. The therapy was documented for 1 month with the initial 10 days as in-patient phase. Examinations by physicians were made at the end of hospitalisation and after 1 month.

Evaluation criteria

The patients were advised and instructed to keep a diary for urinary function. Criteria for analysis were i) spontaneous elimination of calculi or method for elimination, ii) prevalence of leucocyturia, iii) diuresis (volume measured by patients with graduated vessels and documented in the diary, iv) urine pH (measured with test strips at



A stone in the right ureter. CT with contrast medium.

each visit by the physicians), and v) tolerability of the herbal therapy. Urinary calculi were located and measured by ultrasonography and/or intravenous urography. Spontaneous (natural) elimination of concrements as well as presence of leucocyturia was measured during hospitalisation. Urine pH was determined at study initiation and after 1 month of therapy. Tolerability of the herbal medicinal product was evaluated by documentation of adverse events, conspicuous laboratory findings, vital signs and physical examinations.

Statistics

Data from all patients enrolled into one of the study group were included in the efficacy as well as the safety evaluation. Data analysis was performed by descriptive statistical methods.

Results

Demographic data: A total of 237 patients was included. 135 patients were randomized to the herbal combination plus standard medication (study group) and 102 patients to the standard medication (control group) (Tab. 1). All patients hospitalised and fulfilling the inclusion criteria were randomised to the study groups. As there were no drop-outs, the evaluation could be done for all patients.

Depending on the location of renal or urinary concrements and/or calculi, patients of the study and the control group were classified into 4 sub-groups (Tab. 2).

Efficacy

The spontaneous elimination of concrements within the first 10 days of treatment was higher in the study group: The fre-

Tab. 1: Demographic data.

Criteria	Canephron group (n = 135)	Control group (n = 102)
Age	47 ± 5.8 years (range 28–56)	44 ± 6.4 years (range 29–61)
Gender	81 male, 54 female	57 male, 45 female
Leucocyturia	87 patients (64.4%)	45 patients (44.1%)

Tab. 2: Distribution of patients in both groups in respect to localisation of renal und ureteral calculi.

Location of calculi	Study group (herbal combination plus standard medication)		Control group (standard medication)	
	n	average size of calculi [mm]	n	average size of calculi [mm]
Group A – renal calculi (micronephrolithiasis)	66 (48.9%)	4.87 ± 1.02	36 (35.3%)	4.85 ± 1.05
Group B – upper ureteral calculi	21 (15.5%)	3.12 ± 0.98	24 (23.5%)	3.22 ± 0.92
Group C – middle ureteral calculi	18 (13.3%)	2.67 ± 0.72	15 (14.7%)	2.58 ± 0.84
Group D – low ureteral calculi	30 (22.3%)	2.14 ± 0.97	27 (26.5%)	2.12 ± 0.95

quency of spontaneous elimination in patients with renal calculi (group A) was 72.7% (compared to 33.3% in the control group), in patients with upper ureteral calculi (group B) it was 71.4% (control group 37.5%), in patients with middle ureteral calculi (group C) it was 66.6% (control group 40%) and in patients with lower ureteral calculi (group D) it was 90% (control group 55.5%) (Fig. 1).

Patients who did not benefit from herbal therapy and/or conservative treatment were treated by extracorporeal shock-wave lithotripsy (ESWL), ureteroscopy with lithoextraction or ureteric stent incorporation to eliminate the concrements (stones and calculi) (Tab. 3).

Leucocyturia was present at study initiation in 87 (64.4%) of patients in the herbal

combination group and in 45 (44.1%) of patients in the control group. After 10 days of treatment, in patients with initial leucocyturia it was reduced to 6.9% in the study group but increased to 53.4% in the control group (Fig. 2).

Until the end of the treatment for 1 month there was a remarkable increase of mean daily urine volume in the study group as compared to the control group. Further, in the study group a normalisation of urinary pH-value was noted (Tab. 4).

Tolerability

No adverse drug reactions were reported during the entire study period. Further, there were no safety concerns with regards to laboratory findings, vital signs or physical examinations.

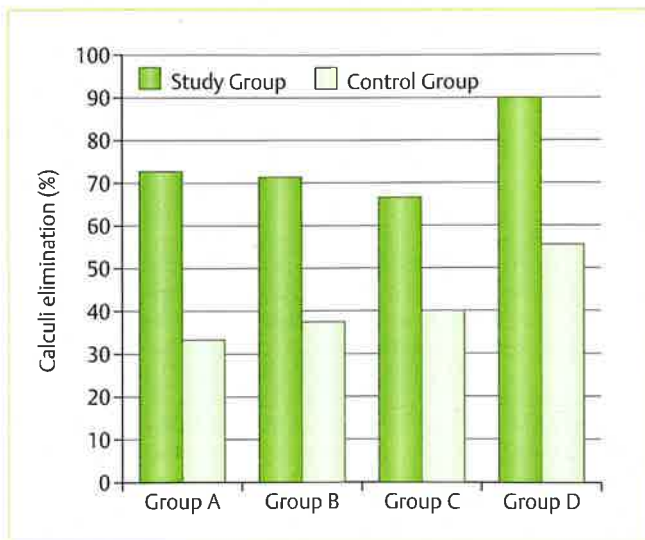


Fig. 1: Spontaneous elimination of calculi within the first 10 days of therapy in both study cohorts (in % of the patients of the subgroups).

Discussion

The study presents supporting evidence of the efficacy and safety of a herbal combination product (Canephron® N) in the add-on treatment of urolithiasis. Regarding the multifactorial causality of stone formation and elimination, obviously several factors of urolithiasis are addressed. The use of the herbal combination product improves the spontaneous elimination of small calculi (0.3–0.6 cm) in reno-ureteral lithiasis, irrespective of their location. This is demonstrated by the increased spontaneous elimination of calculi in the study group, which is superior to the control group. Further, the herbal combination decreases leucocyturia, which is frequently associated with urolithiasis (25). Third, it also seems to improve diuresis facilitating spontaneous elimination of calculi by increased irrigation of the urinary tract.

According to the Guidelines of EAU (6), in patients with newly diagnosed ureteral stones of up to 10 mm where active stone removal is not indicated, observation with periodic evaluations is an option for initial treatment. These patients may be offered appropriate therapy to facilitate stone passage during the observation period, such as the »off-label use« of alpha-blockers and nifedipine (calcium-channel blocker),

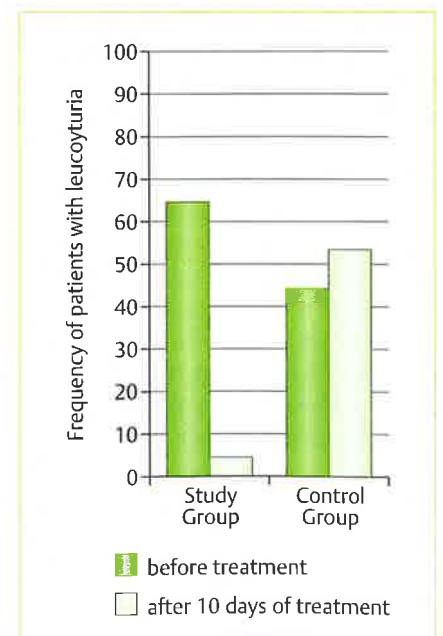


Fig. 2: Incidence of leucocyturia after 10 days of treatment in both study cohorts.

Tab. 3: Method of elimination of calculi in nonresponders to conservative treatment.

	ESWL		Ureterscopy with lithotripsy		Ureteric stent insertion	
	Study group	Control group	Study group	Control group	Study group	Control group
Group A	18 (27.3%)	24 (66.7%)	0	0	0	0
Group B	5 (23.8%)	12 (50.0%)	0	0	1 (4.8%)	3 (12.5%)
Group C	4 (22.2%)	6 (40.0%)	0	1 (6.7%)	2 (11.2%)	2 (13.3%)
Group D	0	7 (25.9%)	3 (10.0%)	4 (14.8%)	0	1 (3.8%)

Tab. 4: Mean daily urinary volume and mean urinary pH-value before and after one month of treatment.

	Study group		Control group	
Daily urine volume [ml]	1378 ± 108	2357 ± 345	1348 ± 132	1838 ± 402
Urinary pH-value	5.6	6.4	5.7	5.8

which may also reduce the need for analgesics due to painful colics. However, patients should be counselled about the attendant risks of such a therapy, including associated drug side effects and they should be informed that it is administered as off-label use (6). Add-on therapy with herbal medicinal drugs such as the presently used herbal drug combination seems to be an effective supportive and also safe alternative.

Pharmacological treatment is necessary in patients with a high risk of recurrent stone formation. Normally, medication is combined with general preventive measures (change and/or control of fluid intake and diet, change of life style). An ideal pharmacological agent should stop stone formation, be free of side effects and easy to administer. Each of these aspects is of utmost importance in order to achieve reasonably good compliance overall (6). The multifactorial efficacy and the good safety profile of the herbal drug combination used in the present study hints to a possible preventive effect, which should be evaluated with follow-up studies.

A limitation of the study was the open study design, therefore placebo effects cannot completely be ruled out.

In conclusion, the results of the present study show that add-on therapy with Canephron® N seems to be effective and safe in reno-ureteral lithiasis. Possible preventive effects should be confirmed in long-term studies.

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ZUSAMMENFASSUNG

Wirksamkeit eines Kombinationsarzneimittels aus *Centaurii herba*, *Levistici radix* und *Rosmarini folium* bei Urolithiasis: Ergebnisse einer offenen, randomisierten, Kohortenstudie

Urolithiasis (Harnsteinleiden; Bildung von Konkrementen in den ableitenden Harnwegen) kann zu schmerzhaften, kolikartigen Schmerzen führen, wenn die Konkreme-
mente oder Steine die Harnwege blockieren. Pflanzliche Drogenzubereitungen spielen seit Langem eine bedeutsame Rolle in der Prophylaxe und Therapie des Harnsteinleidens. In einigen Studien wurde bereits die Wirkung des Phytopharmakons Canephron® N, einer fixen Kombination der Drogen *Centaurii herba*, *Levistici radix* und *Rosmarini folium*, bei der Urolithiasis gezeigt. In einer aktuellen offenen, randomisierten, monozentrischen Kohortenstudie wurde die Therapie mit Canephron® N als Add-on-Therapie untersucht. Das Phytopharmakon wurde 135 Patienten zusätzlich zur Standardtherapie verabreicht, die Daten dieser Kohorte wurden mit den Daten von 102 Patienten unter Standardtherapie verglichen. Canephron® N begünstigte die spontane Elimination von Konkrementen und verminderte die Leukozyturie, die insbesondere mit entzündlichen Prozessen im Harntrakt einhergeht. Die Anwendung der Kombination zur Prävention und/oder als Add-on-Therapie in Ergänzung der Standardtherapie der Urolithiasis erscheint gerechtfertigt.

Schlüsselwörter

Urolithiasis, Phytotherapie, *Centaureum* spp., *Levisticum officinale*, *Rosmarinus officinalis*, offene randomisierte Kohortenstudie, Wirksamkeit

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