Randomized controlled study of the efficacy and safety of product UROLITINN® in the elimination of calculus in patients with renal colic as a consequence of calculi in the ureter

Researcher: Prof. dr Aleksandar Vuksanović

Co-researchers: Ass. dr Uroš Bumbaširević, dr Marko Živković

Institution: Urology Clinics, Clinical Centre of Serbia, No. 51 Resavska, Belgrade, Serbia

INTRODUCTION

Nephrolithiasis is a very common condition with the prevalence of 5-12% in the general population. The disease is recurrent, and in 50% of patients, the recurrence of calculi in the kidney is expected in the first ten years. The last decade has seen an increase in the incidence of this disease in developed countries with higher living standard, primarily due to increased intake of protein foods and minerals.

Calculi in the kidney, ureter and renal colic have a significant impact on the quality of patients' life. Due to the intense pain, these conditions result in frequent visits to emergency medical services, the need for analgesics, antiemetics, absence from work, and they are often a reason for hospitalization, so in addition to health, they represent also a significant socio-economic burden on health insurance systems.

According to the Guides of the European and American Association of Urologists, the spontaneous elimination is expected in 68% of cases when calculus in ureter ≤5 mm is in question, as well as in 47% of cases when the size of calculus is 5-10mm. In cases when spontaneous elimination does not happen or complications occur, there is a need for surgical desobstruction of the urinary system: placement of a ureteral stent or percutaneous nephrostomy catheter, extracorporeal shock wave lithotripsy or in-situ lithotripsy during ureterorenoscopy. All these methods increase the cost of treatment and bear a risk of possible complications. In the case of ureterorenoscopy, the risk of developing sepsis is 4%, and 6% of ureteral injury. For these reasons, stimulation of spontaneous elimination is a benefit for the patient himself because the need for additional expensive interventions that also carry health risks is thus reduced.

Urolitinn® is bioactive herbal complex produced by hydrodistillation of eight medicinal plants (Common Horsetail – Equisetum arvense, Sandwort – Spergularia rubra, Boldo leaves – Peumus boldus, Nopal Cactus – Opuntia ficus-indica, Ironwort flower – Sideritis angustifolia, Rosemary leaf – Rosmarinus officinalis, Bermuda grass – Cynodon dactylon and Lemon balm leaf – Meliisa officinalis) which synergistically have diuretic, antispasmodic, anti-inflammatory and antibacterial effects. Previous studies have shown that this herbal mixture significantly increases diuresis in

subjects with calculi in the renal collecting system or ureter, as well as that it reduces crystalluria, accelerates the elimination of calculus, reducing leukocyturia and bacteriuria at the same time. The use of Urolitinn® has proven to be safe in the previous clinical practice. Severe adverse effects have not been recorded, and tests on a small number of patients have shown excellent tolerance to the product with the sporadic occurrence of mild gastrointestinal disorders that did not require discontinuation of the use of this herbal complex.

Method of administration: twice a day by 30ml (dosing unit included in the pack), dissolve in a half a glass of water and drink, minimum 15 minutes before a meal.

Manufacturer: LABORATORIO MIQUEL Y GARRIGA, S.L., C/Joaquin Costa, 18-10, 08390 Montgat, Barcelona, Spain

Marketing Authorization holder for a dietary supplement: Innventa pharm d.o.o., No. 36/9 Šumatovačka St., 11000 Belgrade, Republic of Serbia

Hypotheses:

1. The use of Urolitinn® accelerates the degree of spontaneous elimination of calculus (stone-free rate) in the ureter and after extracorporeal shock wave lithotripsy (ESWL)
2. The use of Urolitinn® shortens the time required for spontaneous elimination of calculus in the ureter and after extracorporeal shock wave lithotripsy (ESWL)
3. The use of Urolitinn® reduces the intensity of pain due to spontaneous elimination of calculus in the ureter and after extracorporeal shock wave lithotripsy (ESWL)
4. The use of Urolitinn® decreases the need for additional interventions aimed at achieving desobstruction of the urinary system after renal colic and after extracorporeal shock wave lithotripsy (ESWL)

Testing of efficacy and safety of the use of Urolitinn® for elimination of calculi in patients with acute episode of renal colic due to calculi in the ureter.

Inclusion criteria:

1. Patients with an acute episode of renal colic
2. Patients aged 18-65 years
3. Presence of calculus of 4 to 10 mm in size in the ureter diagnosed by native radiography of urogenital tract (native X-ray imaging of urogenital tract)
4. First or second degree hydronephrosis on the ipsilateral kidney diagnosed by renal ultrasonography (ultrasound imaging of urogenital tract)
5. Solitary calculus in any segment of ureter
6. Signed informed consent on participation in the study

Exclusion criteria:

1. Third or fourth degree hydronephrosis diagnosed by renal ultrasonography (ultrasound imaging of urogenital tract)
2. Presence of two or more calculi in the ureter
3. Presence of calculus in the ureter which is bigger than 10 mm or smaller than 4 mm
4. Presence of calculus in the collection renal system, without the calculus in the ureter
5. Presence of bilateral ureteral calculi
6. Presence of calculus in the ureter of the only functional kidney
7. Presence of congenital or acquired urinary tract anomalies (solitary kidney, horseshoe kidney, ectopic kidney, presence of duplicated renal pelvic or ureter systems…)
8. History of previous ureteral stenosis
9. Data on chronic severe renal insufficiency (fourth or fifth degree)
10. Presence of elevated body temperature or urinary infection
11. Previous surgical procedures on the ipsilateral kidney or ureter
12. Female patients in the period of pregnancy, lactation or the ones planning to get pregnant during the study
13. Information on psychiatric or other severe under-treated diseases
14. Presence of hypersensitivity to medicines used in the testing
15. Patients who cannot sign the informed consent

Identification of potential participants in the study:

As a standard practice, patients with an acute episode of renal colic as a result of calculi in the ureter diagnosed with ultrasonography of the abdomen and pelvis (ultrasound imaging) and native radiography of the urogenital tract (native X-ray imaging of urogenital tract) will be offered the opportunity to participate in the study with providing them with all relevant study information. Screening of interested patients will be done in line with the inclusion and exclusion criteria. Upon the decision to participate in the study, patients will be given informed consent to sign, after which

randomization will be performed in accordance with the algorithm of the internet-available randomization calculator. (https://www.graphpad.com/quickcalcs/randMenu/). Patients will be randomized in two groups of subjects, first – which will be made of subjects who will receive the active treatment with the product Urolitinn® and second – active follow-up will be done in this group of subjects.

Follow-up of subjects:

The goal is to recruit 40 subjects, 20 of them will form the first group and receive the product Urolitinn® (in a standard dose of 30 mL twice a day, dissolved in half a glass of water and administered 15 min before meals), and 20 subjects who will be actively followed up in anticipation of spontaneous elimination of calculus. Apart from the product Urolitinn® or active follow up, the subjects will be allowed also to use analgesic Diclofenac. Follow-up of all subjects is planned over the period of 28 days, i.e. until the spontaneous elimination of calculus or clinical assessment on the need for surgical desobstruction or drainage of renal collecting system. During screening and follow-up of the subjects, the basic clinical and demographic characteristics of the subjects, anamnestic data will be collected, physical examination by systems will be done, ultrasonography and native radiography of the urogenital tract (native X-ray of the urogenital tract) will be made, pain intensity will be analyzed by VAS scale and the use of the recommended analgesic will be assessed.

Subjects follow-up regimen:

Follow-up day	Anamnesis	Physical examination	Blood test results	Urine sediment	Ultrasound	X-ray of urogenital tract	VAS pain scale	Questionnaire on the quality of life	Assessment of the analgesic use
Screening	+	+	+	+	+	+	+	+	-
Day 7	+	+	-	-	+	+	+	+	+
Day 14	+	+	-	-	+	+	+	+	+
Day 21	+	+	-	-	+	+	+	+	+

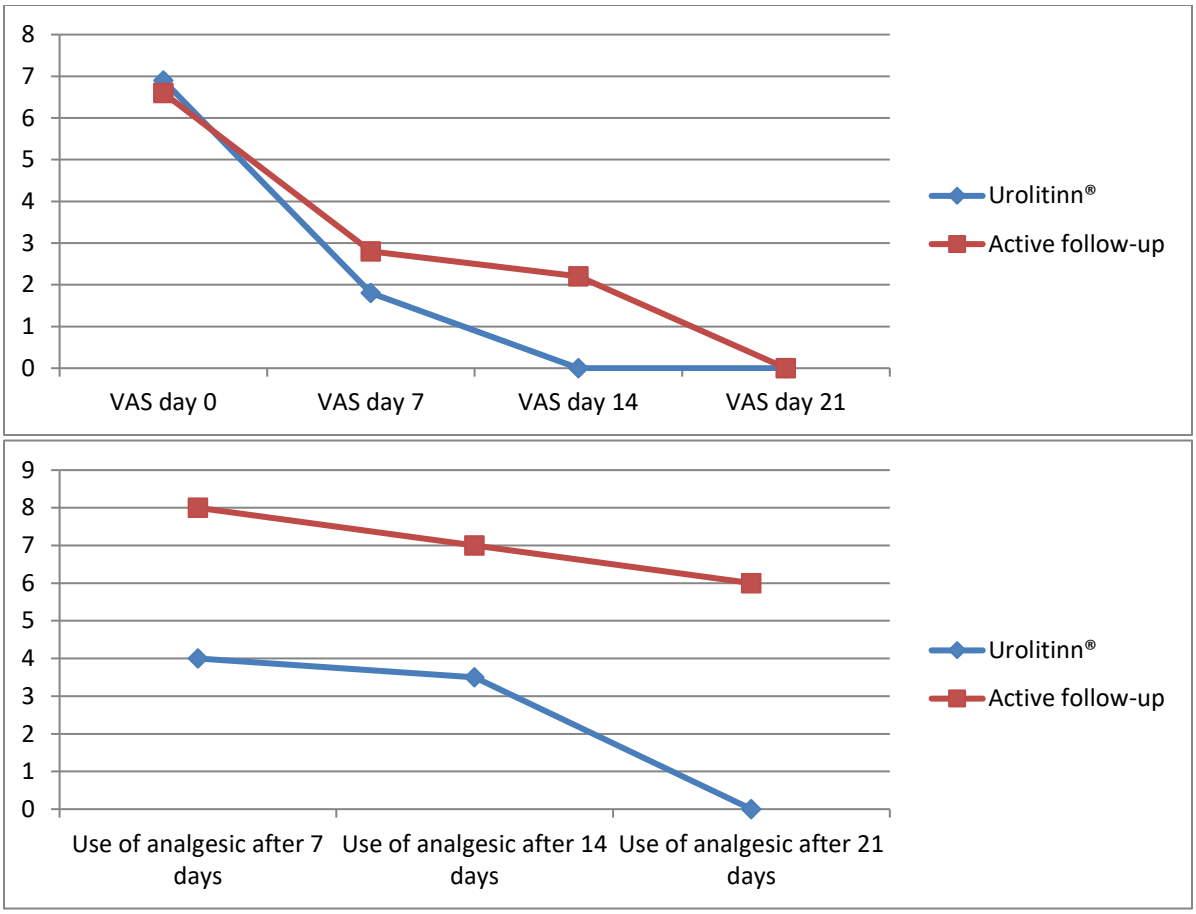
Randomized controlled study of the efficacy and safety of the product UROLITINN® in the elimination of calculus in patients with renal colic as a consequence of calculi in the ureter

Introduction: Nephrolithiasis is a very common condition with the prevalence of 5-12% in the general population. The disease is recurrent, and in 50% of patients a recurrence of kidney calculus is expected in the first ten years. The last decade has seen an increase in the incidence of this disease in developed countries with higher living standard, primarily due to increased intake of protein foods and minerals. Calculi in the kidney, ureter and renal colic have a significant impact on the quality of patients' life. Due to the intense pain, these conditions result in frequent visits to emergency medical services, the need to use analgesics, antiemetics, absence from work, and they are often a reason for hospitalization, so in addition to health, they represent also a significant socio-economic burden on health insurance systems. **Urolitinn®** is bioactive herbal complex produced by hydrodistillation of eight medicinal plants (Common Horsetail – Equisetum arvense, Sandwort – Spergularia rubra, Boldo leaves – Peumus boldus, Nopal Cactus – Opuntia ficus-indica, Ironwort flower – Sideritis angustifolia, Rosemary leaf – Rosmarinus officinalis, Bermuda grass – Cynodon dactylon and Lemon balm leaf – Meliisa officinalis) which synergistically have diuretic, antispasmodic, anti-inflammatory and antibacterial effects. Previous studies have shown that this herbal mixture significantly increases diuresis in subjects with calculi in the renal collecting system or ureter, as well as that it reduces crystalluria, accelerates the elimination of calculus, reducing leukocyturia and bacteriuria at the same time. The use of **Urolitinn®** has proven to be safe in the previous clinical practice. Severe adverse effects have not been recorded, and tests on a small number of patients have shown excellent tolerance to the product with the sporadic occurrence of mild gastrointestinal disorders that did not require discontinuation of the use of this herbal complex.

Material and methods: 40 patients with radiographically confirmed renal colic (by ultrasound examination of abdomen and small pelvis and native radiography of urogenital tract) participated in our study. After being told about the opportunity to participate in the study, patients signed the informed consent and were then randomized into two groups - the first, consisting of 20 subjects receiving the product **Urolitinn®** and the recommended analgesic (Diclofenac tablets or suppositories at a dose of 50 mg), while the second group consisted of 20 subjects who were actively followed up with the recommended analgesic. All the subjects were followed up over a period of 28 days, i.e. until the moment of spontaneous elimination of calculus or clinical assessment on the need for surgical desobstruction or drainage of the renal collecting system. During screening and follow-up of the subjects, the basic clinical and demographic characteristics of the subjects, anamnestic data were collected, physical examination by systems was done, ultrasonography (ultrasound imaging) of abdomen and small pelvis was done as well as native

radiography of urogenital tract (native X-ray imaging of urogenital tract), pain intensity was analyzed by the VAS scale as well as the need for analgesics.

Results: The average age of the first group was 47 years, while the average age in the second group was 48 years. The average size of calculus in both groups of subjects was 6.2 mm, in the first group from 5-8 mm, and in the second group from 5-7 mm. The spontaneous elimination of calculus was achieved in the first group of subjects in all cases during the follow-up period (on average during 9.3 days) - stone free rate 100%, while in the second group of subjects, spontaneous elimination was achieved in 19 patients (stone free rate 95%, 19.6 days passed on average until spontaneous elimination) while one patient was sent after the follow-up period to endolithotripsy of the calculus in the ureter. Pain intensity measured by VAS scale was on average 6.9 in the first group during the first examination (at the scale from 1-10), while it was 6.6 in the second group. After seven days the intensity of pain was lower on average in the first group of subjects (1.8) compared to the second group of subjects (2.8), and after 14 days, the elimination of calculus was achieved in the first group of subjects so none of the patients reported the presence of pain (VAS 0), while in the second group the pain was 2.2 according to VAS. During the follow-up period, greater use of analgesics was noted in the second group of subjects. The value was expressed as the average number of used tablets/suppositories per patient in each group of subjects at the weekly level. After seven days analgesic was used on 4 occasions in the first group of subjects (8.8 in the second group), 3.5 times in the first group of subjects after 14 days and 7 times in the second group of subjects, while after 21 days there was no need to use analgesics in the first group of subjects, while it was used for 6 times in the second group.



Conclusion: High percentage of spontaneous elimination of calculus was achieved in both groups of subjects. The spontaneous elimination of calculus was achieved faster on average in patients who administered the product **Urolitinn®** than in the group of subjects who were subjected to active follow-up. Also, analgesic was less needed in the first group of subjects and the intensity of pain was lower accordingly.