THE EFFECTIVENESS OF RENALOF® COMPARED TO KALKURENAL® AND PLACEBO

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ABSTRACT

Objective: *To compare the effectiveness after administration of Renalof® to Kalkurenal ® and placebo in patient with renal calculus.* ***Material & Method:*** *We analyzed 30 patient with renal calculi less than or equal to 20 mm (2 cm) between January 2011 and March 2011. Patients were divided into 3 groups. Nine patients were treated with placebo, 8 patients were treated with Kalkurenal® and the last 13 patients were treated with Renalof®. After 30 days, we analyzed calcium and uric acid excretion for 24 hours and measured the stone with plain abdominal film and renal ultrasound.* ***Results:*** *There were decreased in excretion of calcium and uric acid all of patients but not significant statistically ($p > 0,05$) and there were significant decreased on stone measurement in patient treated with Renalof®.* ***Conclusion:*** *Renalof® can be given as adjunct therapy for patient with renal calculi.*

Keywords: *Calcium excretion in urine 24 hours, uric acid excretion in urine 24 hours, stone measurement, stone surface area.*

ABSTRAK

Tujuan Penelitian: *Membandingkan efektifitas pemberian Renalof® pada pasien dengan batu ginjal dibandingkan Kalkurenal® dan Plasebo.* ***Bahan & Cara:*** *Dilakukan uji klinis pada 30 pasien dengan ukuran batu ginjal $\leq$ 20 mm (2 cm) antara Januari sampai Maret 2011. Pasien dibagi atas 3 kelompok, yaitu 9 pasien mendapat plasebo, 8 pasien mendapat Kalkurenal® dan 13 pasien mendapat Renalof®. Penelitian dilakukan selama 30 hari. Pada akhir penelitian dilakukan analisa eksresi kalsium dan asam urat dalam urine selama 24 jam dan analisa ukuran batu dan luas permukaan batu berdasarkan foto polos perut dan ultrasonografi urologi.* ***Hasil Penelitian:*** *Terjadi penurunan eksresi kalsium dan asam urat dalam urine selama 24 jam pada semua kelompok meskipun tidak bermakna ($p > 0,05$) dan penurunan ukuran batu dan luas permukaan batu yang bermakna ($p < 0,05$) setelah pemberian Renalof®.* ***Simpulan:*** *Pemberian Renalof® dapat digunakan sebagai pendamping dan bukan pengganti pengobatan pada pasien dengan batu ginjal ukuran $\leq$ 2 cm.*

Kata Kunci: *Ekskresi kalsium dalam urine 24 jam, asam urat dalam urine 24 jam, ukuran batu, luas permukaan batu.*

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INTRODUCTION

Urinary tract stone disease is the third most common urinary tract abnormality after urinary tract infections and prostate disorders. Without medical intervention and reliable follow-up, the recurrence rate may reach 50% within 5 years.[1] The prevalence of urinary tract stones in the world is estimated with lifetime incidence of 10-15% with a recurrence rate of 10% in 1 year, 35% in 5 years and 50% in 10 years.[2] In Indonesia, urinary tract stone disease is still the largest number of patients in urology clinic with the uncertain incidence.[3] At the Urology Department, Dr. Soetomo Hospital Surabaya, urinary tract stone disease is second in number of cases only to prostate disease, with 577 cases/year.[4]

Urinary tract stone recurrence rate is high enough to cause certain problems in terms of health financing. In the United States, urinary tract stone disease raises problems in health budget, with cost 2,1 billion dollars per year.[5] Lost work time, hospitalization and surgery in patients with kidney

stones spend 5 billion U.S. dollars each year,[6,7] with peak incidence in age group 20-50 years,[8] and the ratio between men and women is 3 to 1.[9] This suggests that the disease often affects productive age group.

Until now the management of patients with kidney stones include conservative measures, medical, minimally invasive, ESWL and open surgery. Role of phytopharmaceuticals in the treatment of kidney stones is still under debate and has not been a gold standard. Kidney stones are complex, because the process of its formation is still uncertain. In addition to dietary modifications and adequate hydration, the use of phytopharmaceuticals continues to grow. Certain phytopharmaceuticals claim effectiveness in kidney stones and are widely distributed. However, the research and clinical publications about those drugs are still very limited. Kalkurenal is a phytopharmaceutical that claims to destroy kidney stones and it has been distributed in Indonesia for a long time. Many clinicians prescribe it. Renalof® is a new product in Indonesia that is effective to destroy calcium oxalate renal calculi. As known in the literature, approximately 80% of the composition of the stone is calcium oxalate.[10] Wibisono conducted a retrospective study on 154 kidney stone patients in Dr. Soetomo Hospital Surabaya between 2007-2009 and the analysis results revealed 87,67% stones with calcium oxalate.[11]

Several studies have been conducted on Renalof®, including 1) A study by Dr. Med. Constantin Nitoiu, Romania in 2005 under the title "The treatment of renal lithiasis and microlithiasis with RENALOF® preparation", 2) Research by Professor Mayra, Havana in 2008, a Clinical trial entitled "Treatment of renal lithiasis with food supplement Renalof", 3) Research by Aties M, Cuban Institute of Nephrology in 2009 under the title "Double-blind randomized study: Efficacy and safety of Renalof® in the treatment of patient carrier of calcium oxalate renal lithiasis". Of the three studies, Renalof® is effective in kidney stones with a size less than 20 mm, and decline in the size of the stones had been seen in one month administration.

Metabolic risk factors also play a role in the formation of kidney stones such as hypercalciuria, hyperuricosuria, hyperoxaluria, hypocitraturia, low levels of magnesium and stone inhibitor deficiency. 30-60% of nephrolithiasis patients were with hypercalciuria and 15-20% with hyperuricosuria.[12]

High recurrence rate also poses particular problems in terms of health financing. In the United States, urinary tract stone disease raises a problem in health budget, with a cost of 2,1 billion dollars per year.[5] Lost work time, hospitalization and surgery in patients with kidney stones spend 5 billion U.S. dollars each year,[6,7] while in Indonesia it is still not determined.

This study compared the stone-free rate of kidney stone patients with a size less than 20 mm after Renalof ® administration compared to Kalkurenal ® and placebo for 1 month.

OBJECTIVE

Comparing the effectiveness of Renalof® in patients with kidney stones compared to Kalkurenal® and placebo.

MATERIAL & METHOD

This study used double-blind prospective clinical study design conducted from January – March 2011 in Dr. Soetomo Hospital, Surabaya.

The samples in this study were randomly allocated into 3 groups, each group of 8 persons, namely group 1 (control group with placebo), group 2 (group treated with Kalkurenal®) and group 3 (group treated with Renalof®). All patients enrolled had a single kidney stone with largest diameter ≤20 mm.

Furthermore, examination on the patient was done for the urinary profiles of calcium, uric acid, phosphate, urine pH and urine volume for 24 hour, and then the serum measurements of calcium, uric acid, phosphate and stone analysis. Early imaging was performed, presenting as plain abdominal radiograph, renal ultrasonography and IVP. After undergoing treatment with placebo, Renalof® and Kalkurenal® for 4 weeks, we evaluated plain abdominal radiograph and renal ultrasound in week 4. The patients were examined for profiles of calcium, uric acid, phosphate and urine volume capacity of 24-hour collected urine and the profiles of calcium, uric acid, and phosphate in blood.

The analysis was descriptive and analytic. Comparison test was performed on three sample groups of using the paired Student t-test for comparing the three groups and the data were nominal. Testing of data homogeneity and normality of data using ANOVA and the Kolmogorov-Smirnov test and regression analysis were performed.

Statistical tests with commercial statistical software package.

RESULTS

Baseline demographic characteristics of the sample with enrolled samples of 30 patients and 38 renal units are shown in table 1. There were 14 men and 16 women. Mean body mass index was 26,08 ± 2,86; classified as overweight (BMI 25 to 29,9). Most of the stones were located in the right kidney, comprising 22 renal units (57,89%) and most of the stones position was at middle pole of the kidney, comprising 23 renal units (60,53%). Most were stones with a size of 6-9 mm (44,74%).

In Table 2 the most frequent stone location was at the center pole (60,53%) and lower pole (39,47%), and stones were more frequently observed in the right kidney than the left kidney (57,89% vs. 42,11%).

The results of stone analysis showed that the calcium and oxalate were the most common components (33,48 ± 8,87 vs. 38,78 ± 16,67) followed by uric acid (12,78 ± 12,50). The most

Table 1. Demographic characteristics of the study.

Parameter	Placebo	Kalkurenal®	Renalof®
Total Patients (n)	9	8	13
Total renal units (n)	10	9	19
Male/Female (n)	5/4	4/4	5/8
Age (mean SD)	50,56 9,697	54,13 10,02	45,31 10,55
IMT (mean SD)	25,58 2,05	27,5 3,36	25,55 2,92
Stone size (mean SD)	5,8 1,93	8 2,74	7,32 2,83
Stone surface size (mean SD)	0,22 0,8	1,10 1,92	3,98 5,84
Lateralization (n renal unit = 38)			
Right kidney stone	6 (15,79%)	4 (10,53%)	12 (31,58%)
Left kidney stone	4 (10,53%)	5 (13,52)	7 (18,42%)
Stone position (n renal unit = 38)			
Upper pole	0	0	0
Middle pole	8 (21,05%)	7 (18,42)	8 (21,05%)
Lower pole	3 (7,89)	2 (5,26%)	10 (26,31%)
Stone size in renal USG (n renal unit = 38)			
= 5 mm	5 (13,56%)	1 (2,63%)	7 (18,42%)
6-9 mm	4 (10,53%)	5 (13,16%)	8 (21,05%)
10-20 mm	1 (2,63%)	2 (5,26%)	5 (13,16%)
24-hour urine excretion			
24-hour calcium excretion (mean SD) mg	141,6 60,65	175,69 96,38	166,2 68
24-hour uric acid expression (mean SD) mg	448,28 244,31	508,18 82	462,46 198,88

Table 2. Characteristics of sex, stone position, and location.

Categories		Frequency	Percentage
Sex	Male	14	46,67
	Female	16	53,33
	Total	30	100
Stone location	Upper pole	0	0
	Middle pole	23	60,53
	Lower pole	15	39,47
	Total	38	100
Stone position	Right kidney	22	57,89
	Left kidney	16	42,11
	Total	38	100

common type of stone was calcium oxalate (61,94 ± 21,04) followed by magnesium ammonium phosphate stones (23,33 ± 24,82) and uric acid (13,40 ± 14,12).

Table 3 shows the decline in blood calcium in the three treatment groups, whereas in Renalof® and Kalkurenal® groups there was a significant decrease ($p = 0,015$ and $p = 0,045$; $p < 0,05$).

Table 4 shows none of the three treatment groups had decreased significant of blood uric acid ($p > 0,05$), whereas in Table 5 none of the significant decrease in all three treatment groups ($p > 0,05$).

There was an increase in urinary excretion of uric acid in Kalkurenal® group (table 6), and a decrease in urinary excretion of uric acid in Renalof® group, but the differences did not seem significant ($p > 0,05$).

Apparently, there was a decrease in the surface area of the stones in all three treatment groups (Table 7), but there was a significant reduction in Renalof® group ($p = 0,01$; $p < 0,05$).

Table 3. Paired sample test of blood calcium profile at the early and end of week 4.

	Placebo	Kalkurenal®	Renalof®
Mean	10,133	1,0875	0,507
Standard Deviation	31,24	0,9627	0,820
p	0,359	0,015	0,045

Table 4. Paired sample test of blood uric acid at the early and end of week 4.

	Placebo	Kalkurenal®	Renalof®
Mean	0,469	0,4687	0,028
Standard Deviation	1,163	1,1628	2,067
p	0,292	0,292	0,962

Table 5. Changes in 24-hour calcium excretion of at the start and end of week 4.

	Groups		
	Placebo	Kalkurenal®	Renalof®
Early week 1	141,60 ± 60,64	175,69 ± 96,36	166,20 ± 68,00
End week 4	110,22 ± 28,93	132,06 ± 75,02	151,49 ± 163,63
Delta	31,37 ± 76,95	43,63 ± 61,64	14,71 ± 169,13
p	0,256	0,085	0,759

Table 6. Changes in 24-hour uric acid excretion at the start and end of week 4.

	Groups		
	Placebo	Kalkurenal®	Renalof®
Early week 1	448,28 ± 244,31	508,19 ± 82,00	462,46 ± 198,87
End week 4	344,30 ± 83, 22	656,92 ± 421,57	453,00 ± 250,88
Delta	103,92 ± 253,21	148,74 ± 356,55	9,46 ± 282,86
p	0,253	0,277	0,906

Table 7. Paired sample test the surface area of the stones at the start and end of week 4.

	Placebo	Kalkurenal®	Renalof®
Mean	0,388	4,30	6,46
Standard Deviation	1,056	6,30	6,30
p	0,334	0,095	0,01

Table 8. Paired sample test on the mean size of the stone in USG at the start and end of week 4.

	Placebo	Kalkurenal®	Renalof®
Mean	0,100	0,111	1,210
Standard Deviation	0,568	0,600	2,123
p	0,591	0,594	0,023

Table 9. Differences in stone-free rate in placebo, Kalkurenal® and Renalof® at week 4 (n = 38).

Free stone incidence	Groups		
	Placebo (n - 10)	Kalkurenal® (n - 9)	Renalof® (n - 19)
Free stone	1 (2,63%)	0	3 (7,89%)
Residual stone	9 (23,68%)	9 (23,69%)	16 (42,11%)
Total	10 (26,31%)	9 (23,69%)	19 (50%)

In Table 8 there is significant reduction in the size of the stones on Renalof® group ($p = 0,023$; $p < 0,05$).

DISCUSSION

In this study age distribution of the samples according to treatment groups was homogeneous ($p = 0,159$; $p > 0,05$), and age distribution of the sample revealed normal distribution ($p = 0,963$; $p > 0,05$). Profiles of calcium and uric acid in 24-hour urine in each treatment group showed no significant relationship ($p = 0,870$; $p = 0,226$; $p > 0,05$).

Sample were obtained from the youngest age of 30 years and the oldest 68 years (age range 30-68 years). The mean age of the study sample was 49,23 ± 10,5 years. From a total of 30 patients enrolled, 14 patients were male (46,67%) and 16 were female (53,33%). According to age groups, 14 patients (46,67%) were more than 50 years of age. From the last level of education, most patients graduated from high school, comprising 11 patients (36,67%) followed by primary school of 8 patients (26,67%). The mean body mass index was 26,08 ± 2,86; from which 46,67% were overweight and 10% with obesity.

Urinary tract stone disease is common in productive age group, but this figure will be balanced in women after reaching the age of menopause, presumably because of hormonal influences in which estrogen is protective. This study revealed almost balanced figure because majority of the samples aged over 50 years. A total of 23 patients had performed treatment, in which 12 patients performed PCNL and 11 patients performed open surgery with residual stones less than 20 mm and ESWL was performed once.

Urinary tract stone disease is more frequent in men than in women, in which men 2 to 3 times more likely to suffer from the disease. Presumably this is related to an increase in serum testosterone levels, which leads to increased endogenous production of oxalate. In women and children, serum testosterone levels is low, so the risk of stone is also low.[2]

From the analysis stones, we found components of calcium stone of 33,48% and oxalate of 38,47% with calcium oxalate stone composition of 61,94%. It was not much different from a retrospective study by Wibisono (2011) who obtained the composition of calcium oxalate stones by 87,67%.[11]

Hypercalciuria (calcium excretion > 250 mg/24 hours) was found in 30-60% of the patients with kidney stones, and about 15-20% were found with hyperuricosuria (uric acid excretion > 600 mg/24 hours). In patients with kidney stones, either the first or recurrent, metabolic evaluation is necessary. Examination of 24-hour urine excretion is also reasonably cost-saving. This is important because the risk of first time stone recurrence in the patients can reach 50% within 5 years. In this study no dietary intervention was given, and all samples revealed hypercalciuria urinary calcium excretion of more than 200 mg/day. Approximately 10% of patients with calcium stones had hyperuricosuria. Hypercalciuria and hyperuricosuria are the risk factors for the onset of metabolic stone and should be investigated further. In this study in all treatment groups had decreased excretion of urinary calcium and uric acid, but not significant ($p > 0,05$).

Stone size and stone surface area are important factors in achieving stone clearance. In this study there was significant decrease in the diameter of the stone and the stone surface area after Renalof administration ($p < 0,05$). From the composition of stone samples, it was found that the predominant was calcium oxalate stones. In other words, Renalof administration is effective in patients with calcium oxalate stones.

Phytotherapy with plant medicine is widely used and accepted as an alternative treatment in primary prevention level. In general, herbal medicine for urinary tract stone works through anti-inflammatory effects, diuretic properties, litholytic, anti-microbial and spasmolitic.

Rock fragments of 4 mm was expected to come out spontaneously without the need for interventions, so that it is defined as clinically insignificant residual fragments.[13] The problem will arise how long the spontaneous expulsion is reached. Because these fragments are fixed, it will be potential to grow and become clinically significant. Osman et al (2005) followed-up 173 CIRF patients for 5 years after ESWL. They had residual stones after ESWL up to 3 months in 24-36% of cases, and re-growth was found at 21,4% of patients.[13] Buchholz et al reported the low re-growth rate (2%) at follow-up for 2,5 years, while Kaitan et al reported a greater number (59%) at follow-up of 15 months.[14] In his research Osman and Knoll obtained stone clearance of 98% in the first 12 weeks.[13] Such inconsistent figures are probably because residual stone also lied at lower calyx and the influence of gravity caused low stone clearance. Murphy et al recommended prophylactic therapy in lower calyx asymptomatic kidney stones with size > 1 cm because their observations showed that the probability of being symptomatic was 47% within 2 years.[15]

CONCLUSION

The administration of Renalof® can be used as a complement, not a substitute for treatment in patients with kidney stone sized 2 cm.

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