นิพนธ์ต้นฉบับ

Efficacy of *Orthosiphon aristatus* and Norfloxacin in the Treatment of Patients with Multiple Chronic Health Complaints under Restriction of Purine-rich Food

Amorn Premgamone*
Pote Sriboolue**
Srinoi Maskasem*
Wattana Ditsatapornchareon

Abstract

Nephrolithiasis in northeastern Thailand frequently presents with multiple chronic health complaints (MCHC), namely, myofascial pain, back pain, dyspepsia, arthralgia, headache, fatigue, frank paresthesia, dysuria, and any of these aggravated by purine-rich food (PRF). We previously reported that long-term consumption of *Orthosiphon aristatus* (Blume) Miq. (OA) herbal tea could relieve certain health complaints and cause some reduction of stone size in nephrolithic patients with MCHC and positive white blood cells (WBC) in the urine. The objective of this study was to compare the efficacy of OA or OA plus norfloxacin (NFL) in the treatment of MCHC subjects with negative or positive urine white blood cells. A double-concealed, randomized, controlled trial was conducted in 15 rural villages in Khon Kaen Province from February through July 2005 on 209 MCHC subjects enrolled and 193 evaluated (75 without WBC and 118 with WBC), and randomly assigned into 4 groups, as follows: G1 (39), G2 (36), G3 (60) and G4 (58). Placebo with OA (extract of 1.7 g dried leaves), norfloxacin 400 mg (NFL) and OA+NFL, all in identical capsules, were given to G1, G2, G3 and G4, respectively. The medications were packed, then their codes were concealed. Every group was instructed to avoid purine-rich food (PRF) during the two-week treatment period. Therapeutic success, defined as the reduction of the VAS score ≥50 percent in ≥50 percent of the subjects, for each active MCHC symptom. The results showed subjects in every group reduced their PRF intake during treatments by 90 percent and each active symptom was significantly decreased ($p<0.001$, Friedman Test); thus, therapeutic success was reached within two weeks. A statistically significant difference between the groups was not found. Only the reactive MCHC symptoms of the subjects in G1 (placebo group) did not decrease, while those in the other groups (G2, G3, G4) significantly decreased ($p<0.05$, Pearson chi-square). The study concluded that PRF-restriction significantly reduced MCHC symptoms among all treatment groups within two weeks and the incidence of the reactive MCHC symptoms of G2, G3 and G4 were significantly reduced in the second week while they did not decrease in the placebo group (G1).

Key words: **norfloxacin, *Orthosiphon aristatus*, purine-rich food, chronic health complaints, renal stone**

* *Department of Community Medicine, Faculty of Medicine, Khon Kaen University,*
** *Department of Biochemistry, Faculty of Medicine, Khon Kaen University, Khon Kaen Province*

Background and Rationale

Depending on screening instruments and location, the prevalence of renal stones (RC) among rural dwellers in northeastern Thailand[1,2] varies from 0.38 to 16 percent. Persons with nephrolithiasis usually have multiple chronic health complaints (MCHC), including myofascial pain, back pain, dyspepsia, polyarthralgia, headache, fatigue, frank paresthesia, dysuria at least once a year, and/or any of these made worse by consuming purine-rich foods (PRF).[3] Those complaints (except headache) have been significantly associated with findings of renal stones detected by ultrasonography[4] and present commonly at subdistrict health centers and community hospitals, where MCHC patients make repeat visits for treatment of each symptom separately rather than for the whole syndrome, thereby overburdening the healthcare system.

A study revealed that the higher levels of PRF are associated with an increased risk of gout, whereas a higher level of consumption of dairy products is associated with a decreased risk.[5] Moderate intake of purine-rich vegetables or protein is not associated with an increased risk of gout.

Whether or not white blood cells (WBC) are present in the urine, RC patients can suffer from MCHC. Some urine "dipsticks" can detect nitrites and leukocyte esterase and have a high negative predictive value (90-95%) for excluding for urinary tract infection.[6-8] Recently, Thai patients with large renal stones with MCHC were positive for WBC in their urine and were treated with co-trimoxazole for about two months plus Orthosiphon or sodium potassium citrate. More than 90 percent of both groups reported a substantial reduction in myofascial pain, arthralgia, dyspepsia and fatigue, without any other medication. The study revealed the rate of stone size reduction per year after taking *Orthosiphon* and sodium potassium citrate was 28.5 percent and 33.8 percent, respectively[3].

Orthosiphon, found throughout Southeast Asia, has been drunk as an herbal tea for centuries to treat gout, rheumatism, diabetes, hypertension and RC. An *in vitro* study showed that an aqueous extract of *Orthosiphon aristatus* has an antibacterial activity against two serotypes of *Streptococcus mutans* (MIC 7.8-23.4 mg/mL).[9]

To find an effective method to treat the MCHC, we evaluated the effect of OA (G2) vs. placebo (G1) for the treatment of MCHC without urine WBC and OA plus NFL (G4) vs. NFL alone (G3) in MCHC patients with urine WBC. Since PRF can aggravate MCHC, we tested the interventions while subjects abstained from 25 types of PRF common in rural northeastern Thailand.

Methodology

Trial Design, Funding and Ethics Approval

Our study was a prospective, concealed, randomized, controlled trial conducted over a two-week period. The research was supported by Khon Kaen University and the protocol approved by the Ethics Committee of Khon Kaen University (HE471225) in February 2005. Written informed consent was obtained from the patients who met the inclusion criteria. We started recruiting the patients in March 2005 and finished gathering the data in June 2005.

Subjects

Free ultrasound checks for renal stones were announced through local health workers and village headmen in 15 villages. Participants joining the study were interviewed for their chronic health complaints, received an ultrasound examination and underwent urinalysis (using a urine strip). All of the subjects were asked about the presence of nine chronic symptoms: (1) multiple myofascial pain; (2) back or lower abdominal pain; (3) dyspepsia; (4) polyarthralgia; (5) single-side headache; (6) fatigue; 7) frank paresthesia; (8) dysuria at least once a year; and (9) any of

these aggravated by PRF.

The inclusion criteria comprised: (1) patients with RC or those having a hyperechoic focus suspected of being RC; (2) having five or more of the nine MCHC; (3) having at least two active symptoms at the time of study; (4) being between 20 and 65 years of age; and (5) willing to stop eating PRF during the treatment period.

Subjects were excluded if they had (1) a stone obstruction; (2) heart disease; (3) known chronic renal failure; (4) were pregnant; or (5) had any other severe illness. Patients with negative or positive urine white cells, diagnosed by a urine strip read by a portable urine analyzer (UriluxS, Roche, Basel, Switzerland), were categorized as Set 1 or Set 2, respectively (Figure 1).

Randomization

Subjects in both sets were stratified by the number of their active symptoms: those with 2-4 symptoms were assigned to subgroup 1A or 2A and those with more than 4 symptoms to subgroup 1B or 2B. Each member of each subgroup was assigned a running number according to the time of entering the trial.

Patients from 1A and 1B were allocated by block of six to G1 (the placebo group) or G2 (the OA group) while patients from 2A and 2B were allocated to G3 (NFL plus placebo group) and G4 (the OA plus NFL group). Every sixth consecutive participant was enrolled in each subgroup (1A, 1B, 2A, 2B), three subjects were assigned by coin toss to the G1 group and three to G2. Thus, in Set 1 each running number in subgroup 1A and 1B belonged to either G1 (placebo) or G2 (OA) and in Set 2 to either G3 (NFL plus placebo) or G4 (NFL plus OA). The medications were prepared according to the codes before recruitment began; thereafter, the codes were concealed until the data analysis phase.

Treatment

Norfloxacin (400 mg), placebo and OA extract were loaded into identical-looking capsules. Norfloxacin was ground before the capsules were filled.

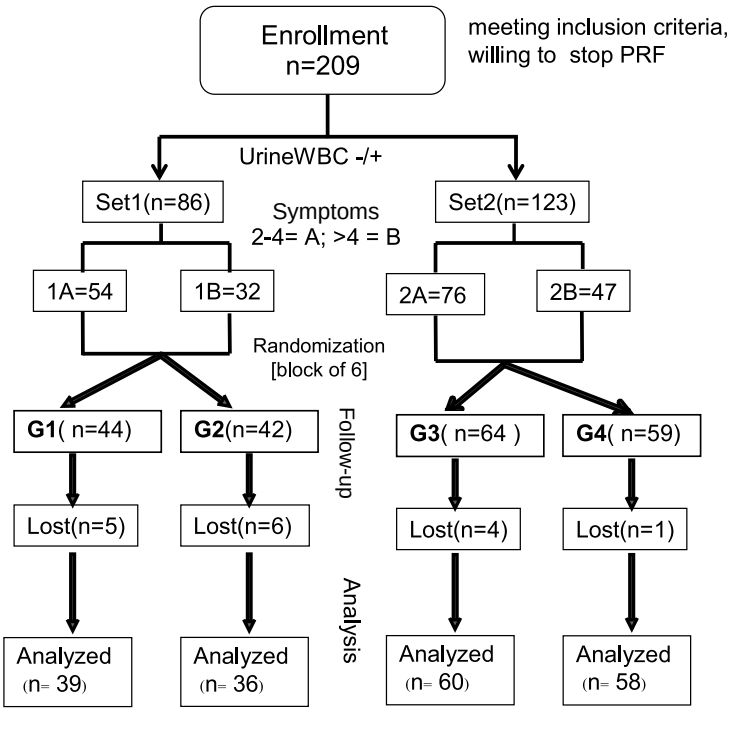

Figure 1 Details of patients enrolled in the study

Table 1 Reasons for losts to follow-up, by treatments

Reason	G1	G2	G3	G4	Total
Side effects	0	2†	1‡	1¶	4
Reactive symptoms	0	2§	0	0	2
Feeling no improvement	3	2	1	0	6
Unknown reason	2	0	2	0	4
Total	**5**	**6**	**4**	**1**	**16**

G1, Placebo; G2, Orthosiphon (OA); G3, Norfloxacin (NFL); G4, NFL +OA
† **palpitation, dizziness**
‡ **palpitation**
¶ **face edema**
§ **fatigue and myofascial pain**

The placebo capsule contained dried, ground swamp morning glory (*Ipomoea aquatica* Forssk). To prepare the OA extract, dried leaves of OA were ground in a mechanical mill and put into hot water (70-80°C) for 20 minutes. The infusion was separated in a container and put into a hot water-bath. The temperature of the infusion was 70-80°C for 36 hours until nearly dried; then it was mixed with a prepared mixture and left in a drying chamber for 48-72 hrs at 40-50°C. This dried mixture was ground and loaded into capsules. Each capsule of OA extract equaled 1.6 to 1.8 g of dried leaves. Set 1 took one capsule of placebo or OA two times a day, while Set 2 took 2 capsules, NFL and placebo for G3 and one NFL capsule and one OA for G4.

Therapies comprised a 20-minute orientation on the schedule and foods that aggravate MCHC to encourage abstention of 25 PRF during the trial period. PRF included bamboo shoots, tops of *Calamus rotang* L., coconut leaf shoots, young leaves of *Acacia pennata,* mushrooms, fermented rice noodle, fermented fruits, fermented vegetables, alcoholic beverages, grasshoppers, red ant larvae, silk worms, crickets, cicada, oxen, buffalo, small freshwater fish, shellfish, squid, fowl, bullfrogs, frogs, frog larvae, and field rats/mice.

Adverse effects of treatments and the reactive symptoms

Adverse effects were defined as new symptoms not on the MCHC list that occurred during treatment. Symptoms already on the MCHC list, inactive at the beginning but becoming active during the treatment, were called *reactive symptoms*.

Measurements

The general feeling of illness (GFI) and each active symptom had a maximum score of 100 and a minimum score of 0, according to the visual analog scale (VAS). VAS was performed by each patient under supervision at the beginning (on day 0) and on days 7 and 14. The percentage reduction in each variable was calculated as follows:

Percentage of score reduction = 100 × [(VAS day 0) − (VAS day 7)] ÷ (VAS day 0)

The main outcome measure was the therapeutic success of each MCHC symptom and the second the therapeutic success in the GFI. The reduction of the score by ≥50 percent in ≥50 percent of the subjects by the fourteenth day was considered a *therapeutic success*. Reduction of the score by ≥25 percent in ≥50 percent of the subjects by day 14 was considered a *partial response*. We otherwise noted a non-response. Data on daily PRF intake were collected retrospectively through interviews on days 0, 7 and 14.

Data analysis

Data were expressed as means and 95 percent confidence intervals (95%CI), medians and interquartile ranges (IQR). A comparison of results between the four groups was performed using one-way ANOVA for normal distributions or the Kruskal Wallis Test for skewed distributions. Before and after analyses within groups was done using the paired t-test or the Friedman test for normal or skewed distributions, respectively. A probability of $p<0.05$ was set for statistical significance.

Table 2 Baseline characteristics and mean scores, by VAS scale, for 193 patients

Variable	Set1 (urine white cell neg.)		Set2 (urine white cell pos.)	
	G1 (n1=39)	G2 (n2=36)	G3 (n3=60)	G4 (n4=58)
Age (>45)	31 (79.5%)	29 (80.6%)	48 (80.0%)	42 (72.4%)
Sex (female)*	27 (69.2%)	22 (61.1%)	54 (90.0%)	48 (82.8%)
Renal stone positive*	28 (71.8%)	23 (63.9%)	54 (90.0%)	53 (91.4%)
Urine RBC found*	7 (17.9%)	9 (25.7%)	25 (42.4%)†	32 (56.1%)†
MCHC* mean (95%CI)	6.6(6.5, 7.6)	6.6(5.9, 7.2)	6.0(5.6, 6.5)	6.3(5.9, 6.7)
GFI score mean (95%CI)	50.3(42.5, 58.1)	52.1(46.5, 57.6)	52.0(47.2,56.7)	50.8(46.3, 55.4)
Active sym mean (95%CI)	4.2(3.6, 4.7)	3.8(3.3, 4.5)	4.1(3.7, 4.5)	4.0(3.6, 4.4)
Myofascial pain n (%)	35 (89.7)	25 (69.4)	43 (71.7)	40 (68.9)
Back pain n (%)	31 (79.5)	30 (83.3)	50 (83.3)	48 (82.8)
Dyspepsia n (%)	15 (38.5)	19 (52.8)	26 (43.3)	31 (53.4)
Polyarthralgia n (%)	27 (69.2)	22 (61.1)	39 (65.0)	40 (68.9)
Headache n (%)	17 (43.6)	10 (27.8)	19 (31.7)	25 (43.1)
Fatigue n (%)	19 (48.7)	14 (38.9)	31 (51.7)	29 (50.0)
Frank paresthesia n (%)	13 (33.3)	12 (33.3)	28 (46.7)	28 (48.3)
Dysuria n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Aggravated by PRF n (%)	35 (89.6)	27 (75.0)	50 (83.0)	49 (84.5)

G1, Placebo; G2, Orthosiphon (OA); G3, Norfloxacin(NFL); G4, NFL+OA;
MCHC, Multiple chronic health complaints; GFI, General feeling of illness; PRF, Purine-rich food;
† exclude menstruation: n3=59, n4 =57;
*** Set1 and Set 2 were significantly different but similar within the sets**

Results

A total of 209 subjects agreed to participate, of whom 5, 6, 4 and 1 were lost to follow-up in G1, G2, G3 and G4, respectively. Two subjects in G2 (with palpitations, dizziness), one in G3 (with palpitation), and one in G4 (with face edema) were excluded because of potential side effects or confounding factors. Two subjects in G2 had reactive symptoms. Three, two and one subjects from G1, G2 and G3, respectively felt unchanged after one week of treatment and then quit. For unknown reasons, two and two subjects from G1 and G3 were lost to follow-up. All 193 subjects mentioned had complete data portfolios and were analyzed on an intention-to-treat basis (Figure 1 and Table 1).

Baseline patient characteristics

The mean age of participants was 53.7 years (53.5, 53.8, 55.5 and 52.0 for G1, G2, G3 and G4, respectively). Table 2 shows the patients' baseline characteristics. They were similar in the percentage of patients aged over 45 years (79.5, 80.6, 80.0 and 72.4%), for the mean (95%CI) of VAS score for GFI [50.3 (42.5,58.1), 52.1 (46.5,57.6), 52.0 (47.2,56.7), and 50.8 (46.3,55.4)], for mean (95%CI) number of active symptoms [4.2 (3.6,4.7), 3.8 (3.3,4.5), 4.1 (3.7,4.5) and 4.0 (3.6,4.4)], and the percentage with a history of symptoms aggravated by PRF (89.6, 75.0, 83.0 and 84.5). Each group had a similar distribution of the active symptoms.

Some variables were similar within the Set but significantly different ($p<0.05$) between Set 1 (G1, G2) and Set 2 (G3, G4), these were female sex (69.2, 61.1 and 90.0, 82.8%); having a positive ultrasound exam for RC (71.8, 63.9 and 90.0, 91.4%); and positive urine

red cells (17.9, 25.7 and 42.4, 56.1%). The respective mean (95%CI) of the MCHC variables was 6.6 (6.5, 7.6), 6.6 (5.9, 7.2), 6.0 (5.6, 6.5) and 6.3 (5.9, 6.7) symptoms per subject, which were similar within the Sets but significantly different between Sets (Table 2).

Main outcomes: each active MCHC symptoms (Table 3)

There were six active MCHC symptoms, namely, myofascial pain, back pain, dyspepsia, poly-arthralgia, headache, fatigue and paresthesia. There was no significant difference between groups of VAS scores for each of the six active MCHC symptoms on days 0, 7 and 14 of treatments. When compared within groups, each of the six active MCHC symptoms had a significantly decreased VAS score ($p<0.001$, Friedman Test) (Table 3).

Using the therapeutic criteria in every MCHC symptom, G1, G2, G3 and G4 had score reductions of ≥50 percent in ≥50 percent of the subjects during the two-week treatment period, so every symptom in each group met with *therapeutic success,* and there was no statistically significant difference between groups when compared at the same periods (Table 3).

There was one variable, *dysuria at least once a year,* among the MCHC that did not present as an active symptom to be monitored in this study, because it occurred for a few hours or a few days. We could not include dysuria in the evaluation process.

Second outcome: the general feeling of illness (GFI)

There was no significant difference between the four groups vis-á-vis the VAS scores or the GFI on days 7 and 14 (Table 4). Comparing day 0 and follow-up on days 7 and 14, there was a significant decrease ($p<0.001$, Friedman Test) in VAS scores for the GFI for every group (Table 3). When using the therapeutic criteria, G3 and G4 had a score reduction of >50 percent in 56.7 percent and 53.4 percent of subjects who met with therapeutic success, while G1 and G2 had a score reduction of >25 percent in 69.2 percent and 61.1 percent indicating a partial response (Table 3-4).

Purine-rich food (PRF) consumption

The mean frequency of PRF consumption per week among the four treatment groups (G1-G4) during the same period, the week before treatment, the first week and the second week of treatment, were not significantly different, but for the frequency within each group at different periods, every group had a significantly reduced frequency ($p<0.001$, Friedman Test).

The respective mean (SD) of PRF consumption for G1, G2, G3 and G4 over the 7 days before treatment was 11.4 (10.2), 14.2 (13.2), 11.7 (9.2) and 12.2 (9.8) times. In the first and second week of treatment the respective mean (SD) of G1, G2, G3 and G4 was 0.9 (3.4), 1.3 (3.7), 0.3 (0.59) and 0.5 (1.0) times and 0.7 (1.1), 1.3 (4.7), 0.5 (1.1) and 0.5 (1.0) times. About one-third of all PRF consumed regardless of treatment group was bamboo shoots, which significantly declined ($p<0.001$, Friedman Test) in the first and second weeks. The data clearly show that the subjects in every group kept their promise to reduce PRF consumption. Every group reduced PRF intake during the first and second weeks to less than 10 percent of the frequencies before treatment.

Adverse effects and reactive symptoms

In the first week, 42 (21.8%) of the subjects reported new mild symptoms of which 1.5 percent were considered adverse effects and 21.2 percent as reactive MCHC symptoms (Table 5). The side effects were rashes and dizziness, while the re-active symptoms included myofascial pain, fatigue, back pain, arthritis, sleep problems, dyspepsia, headache and paresthesia.

The number of subjects who reported new symptoms, both adverse effects and re-active MCHC, in the first and second week of treatment was not significantly different between groups in the same pe-

Table 3 Number and percentage of patients with a reduction in VAS scores by ≥25% and by ≥50% for MCHC symptoms and GFI on day 7 and day 14

Symptoms	Day	Decrease (%)	G1 (%)	G2 (%)	G3 (%)	G4 (%)	P-val§
Back pain***	7	≥25	22 (71.0)	17 (56.7)	26 (52.0)	28 (58.3)	0.41
(N=159, n1=31, n2=30,		≥50	**16 (51.6)**	**15 (50.0)**	16 (32.0)	21 (43.8)	0.26
n3=50, n4=48)	14	≥25	25 (80.6)	20 (66.7)	38 (76.0)	37 (77.1)	0.62
		≥50	**18 (58.1)**	**16 (53.3)**	**30 (60.0)**	**32 (66.7)**	0.69
Myofascial pain***	7	≥25	17 (48.6)	18 (72.0)	25 (58.1)	21 (52.5)	0.98
(N=143, n1=35, n2=25,		≥50	10 (28.6)	8 (32.0)	14 (32.6)	13 (32.5)	0.98
n3=43, n4=40)	14	≥25	26 (74.3)	18 (72.0)	32 (74.4)	30 (75.0)	0.99
		≥50	**20 (57.1)**	**16 (64.0)**	**27 (62.8)**	**21 (52.5)**	0.74
Arthralgia***	7	≥25	14 (51.9)	14 (63.6)	23 (59.0)	23 (57.5)	0.87
(N=127, n1=27, n2=22,		≥50	7 (25.9)	7 (31.8)	16 (41.0)	14 (35.0)	0.64
n3=39, n4=40)	14	≥25	19 (70.4)	15 (68.2)	28 (71.8)	28 (70.0)	0.99
		≥50	**14 (51.9)**	**11 (50.0)**	**23 (59.0)**	**25 (62.5)**	0.73
Fatigue***	7	≥25	9 (47.4)	4 (28.6)	15 (48.4)	18 (62.1)	0.23
(N=93, n1=19, n2=14,		≥50	4 (21.1)	2 (14.3)	11 (35.5)	11 (37.9)	0.29
n3=31, n4=29)	14	≥25	12 (63.2)	9 (64.3)	23 (74.2)	25 (86.2)	0.25
		≥50	**10 (52.6)**	**7 (50.0)**	**20 (64.5)**	**18 (62.1)**	0.73
Dyspepsia***	7	≥25	9 (60.0)	11 (57.9)	16 (61.5)	24 (77.4)	0.42
(N=91, n1=15, n2=19,		≥50	**8 (53.3)**	9 (47.4)	11 (42.3)	13 (41.9)	0.88
n3=26, n4=31)	14	≥25	12 (80.0)	15 (78.9)	24 (92.3)	26 (83.9)	0.59
		≥50	**9 (60.0)**	**12 (63.2)**	**24 (92.3)**	**23 (74.2)**	0.06
Paresthesia***	7	≥25	8 (61.5)	6 (54.5)	17 (60.7)	21 (75.0)	0.56
(N=81, n1=13, n2=12,		≥50	5 (38.5)	4 (36.4)	10 (35.7)	16 (57.1)	0.37
n3=28, n4=28)	14	≥25	11 (91.7)	8 (80.0)	22 (81.5)	24 (88.9)	0.75
		≥50	**9 (69.2)**	**6 (54.5)**	**19 (67.9)**	**21 (75.0)**	0.67
Headache***	7	≥25	11 (64.7)	5 (50.0)	15 (78.9)	17 (68.0)	0.46
(N=71, n1=17, n2=10,		≥50	**10 (58.8)**	3 (30.0)	**14 (73.7)**	11 (44.0)	0.09
n3=19, n4=25)	14	≥25	14 (82.4)	9 (90.0)	17 (89.5)	20 (80.0)	0.79
		≥50	**13 (76.5)**	**5 (55.6)**	**15 (78.9)**	**16 (64.0)**	0.49
GFI***	7	≥25†	20 (51.3)	22 (61.1)	35 (58.3)	34 (58.6)	0.84
(N=193, n1=39, n2=36,		≥50	10 (25.6)	8 (22.2)	20 (33.3)	18 (31.0)	0.64
n3=60, n4=58)	14	≥25‡	27 (69.2)	22 (61.1)	47 (78.3)	44 (75.9)	0.27
		≥50	18 (46.2)	17 (47.2)	**34 (56.7)**	**31 (53.4)**	0.69

G1,Placebo; G2,Orthosiphon (OA); G3, Norfloxacin (NFL); G4, NFL +OA; GFI, General feeling of illness

† **100x (VAS score day 0 – VAS score day 7)/ VAS score day 0**

‡ **100x (VAS score day 0 – VAS score day 14)/VAS score day 0**

§ **between group by Pearson chi-square**

*** **p<0.001, compare VAS score measured on day 0, 7, 14 within group by Friedman test.**

Numbers in bold show score reduction of ≥ 50 percent in 50 percent of the subjects.

Table 4 VAS scores of general feeling of illness for 193 patients by treatments

VAS score of GFI		G1*	G2*	G3*	G4*	P-value‡
Day 0	Median (IQR)†	50.0 (35)	50 (12.8)	51 (17)	50 (18.5)	0.964
	Mean (SD)	50.3 (24.1)	52.1(16.4)	52.1(18.7)	50.6(17.1)	
	95%CI	42.5, 58.1	46.5,57.5	47.2,56.9	46.1,55.1	
Day 7	Median (IQR)†	32.0 (44.0)	34 (20.8)	35 (40)	30 (29)	0.913
	Mean (SD)	36.5 (24.1)	35.5(18.9)	32.6(22.9)	35.9(21.3)	
	95%CI	28.7, 44.3	29.1,41.9	26.6,38.6	30.2,41.5	
Day 14	Median (IQR)†	15 (38.0)	27 (37.5)	20 (28)	20 (31.5)	0.596
	Mean (SD)	26.2 (24.4)	31.3(24.5)	24.5(20.1)	26.1(19.9)	
	95%CI	18.3, 34.1	22.9,39.5	19.0,29.9	20.8,31.4	

G1,Placebo; G2,Orthosiphon (OA); G3,Norfloxacin (NFL); G4, NFL +OA
GFI, General feeling of illness
† Inter-quartile range;
* p<0.001 compared day0 and day7, 14 by Friedman test;
‡ Compared between groups by Kruskal Wallis test.

Table 5 Re-active symptoms and new symptoms in the first and second week

Reported symptoms	Week1†				Week2†			
	G1	G2	G3	G4	G1	G2	G3	G4
Number of subjects‡	7	10	13	12	7	*1	*5	*4
n (%)	(17.9)	(27.8)	(21.6)	(20.7)	(17.9)	(2.7)	(8.3)	(6.8)
New symptom	0	0	1	2	2	0	1	2
Rash	0	0	0	1	1	0	0	1
Dizziness	0	0	1	1	1	0	1	1
Reactive MCHC	7	10	12	12	5	1	4	2
Myofascial pain	4	3	5	8	1	1	1	1
Fatigue	2	4	4	2	1	0	2	0
Back pain	0	2	3	2	2	1	1	0
Arthritis	1	1	3	1	0	0	0	1
Sleep problem	1	2	3	1	0	0	0	0
Dyspepsia	1	1	0	1	3	0	0	2
Headache	1	0	1	1	0	0	0	0
Paresthesia	0	0	1	0	0	0	1	1

G1, Placebo; G2, Orthosiphon (OA); G3, Norfloxacin(NFL); G4, NFL +OA
MCHC, Multiple chronic health complaints
† p >0.1 Compare between groups by Pearson chi-square
‡ Some subjects had ≥1 symptoms
* p<0.05 within group by Pearson chi-square.

riod. The respective percentage of subjects in G1, G2, G3 and G4 who reported new symptoms was 17.9, 27.8, 21.6 and 20.7 percent in the first week and 17.9, 2.7, 8.3 and 6.8 percent in the second. Within the same group between the first and second week, subjects who reported new symptoms decreased significantly in G2, G3 and G4 ($p<0.05$, Pearson Chi-Square), while the subjects in G1 had a similar rate.

The number of subjects who reported myofascial pain decreased from 20 (10.3%) in the first week to 4 (2.1%) in the second. Similarly, fatigue and back pain posted a respective decline from 12 (6.2%) to 3 (1.6%) and 7 (3.6%) to 4 (2.1%).

Discussion

Summary of main findings

When PRF consumption was decreased to <10 percent of the usual level, MCHC symptoms were reduced in all treatment groups. The patients suffering from each of the MCHC symptoms similarly benefited from the four treatments: whether placebo, OA, NFL and NFL plus OA. The severity of each MCHC symptoms decreased ≥50 percent in ≥50 percent of the subjects during the two-week treatment period, and there was no significant difference between the four groups. The severity of GFI in G1 and G2 was reduced less than in G3 and G4, but the difference was not statistically significant when comparing VAS scores ($p<0.596$, Kruskal Wallis Test, Table 3-4). The only difference between groups found in this study was in the incidence of the re-active MCHC in the placebo group (G1), which was not decreased in the second week of treatment, while it was significantly reduced in G2, G3 and G4.

Where this fits with other literature

Without reference to any PRF restrictions, anecdotal reports claimed a good result when people used *Orthosiphon* to treat gouty arthritis, myofascial pain and renal stone. Even though none of these reports were the double-blind randomized controlled trials, most users felt some improvement so they continued using OA. In another study without PRF restrictions,[3] both OA plus co-trimoxazole, and sodium potassium citrate plus co-trimoxazole resulted in a substantial reduction in associated symptoms (i.e., dyspepsia, myofascial pain, arthralgia, back pain) in patient's with nephrolithiasis, positive for WBC in the urine. This information plus results from our study lead us to conclude that: (1) OA or OA plus NFL probably reduces MCHC symptoms more than placebo or placebo plus NFL in patients with or without urine WBC, eating a non-restricted diet; and, (2) with PRF consumption restrictions, the addition of OA or OA and NFL will have no additional benefit over placebo or placebo and NFL in MCHC patients with or without urine WBC.

Strengths and limitations

This was the first Thai study to investigate a method of dealing with MCHC as a syndrome in persons with nephrolithiasis. It was a double-blind randomized controlled trial. The indifferent results of the four treatments actually indicate the primary importance of restricting PRF as the key intervention for resolving MCHC.

There were some limitations to our study. First, 16 (8.2%) subjects refused to continue their medication (Table 1). The authors tried to test the effect of the lost by including the subjects in "not feel improved" and "unknown reason" categories from Table 1 as the subjects with score reduction <25 percent for the general feeling of illness (GFI). Thus, we added 5, 2, 3 and 0 to the number in G1, G2, G3 and G4, respectively. In the recalculation we got the same conclusion for GFI, G1 and G2, that is, a partial response, while G3 and G4 was a *therapeutic success.*

The second limitation was the lack of a control group for PRF restriction, but that is because the testing for the effect of PRF was not one of our original objectives.

Implications

MCHC in the rural community is prevalent, so a method of discovering and treating its root cause would be invaluable. A random survey in the rural communities in Khon Kaen revealed that, during one week, more than 9 out of 10 persons consumed a PRF at least once (i.e., bamboo shoot, fermented food, meat)

and more than one-third reported having their symptoms (myofascial pain, arthralgia, dyspepsia and back pain) aggravated by these foods.[10] Restricting PRF over the two-week research period was practicable for the 193 participants, but would not be easy to maintain much longer as the foods are a main part of the standard northeastern Thailand diet. Nonetheless, the study indicates that MCHC severity could be decreased by restricting the intake of PRF.

In order to compose effective management guidelines for general MCHC patients, the following need answering: (1) Does PRF restriction benefit all MCHC patients even those not aware that they are suffering from nephrolithiasis? (2) Will their symptoms completely disappear if PRF are permanently restricted? (3) Can OA significantly relieve MCHC more than a placebo in patients who do not restrict their intake of PRF? (4) Are there other areas in the world where MCHC prevalence is high and is there an association with gout?

Acknowledgments

This study was supported by Khon Kaen University. The authors would like to thank Mr. Bryan Roderick Hamman for his assistance with the English-language presentation of the manuscript.

REFERENCES

1. Sriboonlue P, Prasongwatana V, Chata K, Tungsanga K. Prevalence of upper urinary tract stone disease in a rural community of northeastern Thailand. Br J Urol 1992;69:240-4.
2. Yanagawa M, Kawamura J, Onishi T, Soga N, Kameda K, Sriboonlue P, Prasongwatana V, Borwornpadughkitti S. Incidence of urolithiasis in northeast Thailand. Int J Urol 1997;4:537-40.
3. Premgamone A, Sriboonlue P, Ditsatapornjaroen W, Maskasem S, Sinsupan N and Apinives C. A long-term study on the efficacy of a herbal plant, Orthosiphon grandiflorus, and sodium potassium citrate in treatment of renal calculi. Southeast Asian J Trop Med Public Health 2001;32:654-60.
4. Premgamone A, Sriboonlue P, Ditsatapornjaroen W, Maskasem S. Distribution of the sizes of kidney stone in a community survey. Asian J Radiol 2008 (in press).
5. Choi HK. Atkinson K, Karlson EW. Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. N Engl J Med. 2004;350:1093-103.
6. Lammers RL, Gibson S, Kovacs D, Sears W, Strachan G. Comparison of test characteristics of urine dipstick and urinalysis at various test cutoff points. Ann Emerg Med 2001;38:505-12.
7. Bonnarddeaux A, Sommerville P, Kaye M. A study on the reliability of dipstick urinalysis. Clin Nephrol 1994;41:167-72.
8. Christenson RH, Tucker JA, Allen E. Results of dipstick tests, visual inspection, microscopic examination of urine sediment, and microbiological cultures of urine compared for simplifying urinalysis. Clin Chem 1985;31:448-50.
9. Chen CP, Lin CC, Namba T. Screening of Taiwanese drugs for antibacterial activity against Streptococcus mutans. J Ethnopharmacol 1989;27:285-95.
10. Premgamone A, Ditsatapornjaroen W, Maskasem S, Kessomboon P. Purine-rich food consumption and its association with subjective health complaints (SHC) in rural villages in Khon Kaen, Thailand. Program and abstract book. WONCA Asia Pacific Regional Conference 2006: Happy and Healthy Family, Bangkok, Thailand; November 5-9, 2006, p. 118.

บทคัดย่อ

สัมฤทธิผลของการรักษาผู้ป่วยอีสานรวมมิตรด้วยหญ้าหนวดแมวและนอร์ฟลอกซาซินในสภาวะควบคุมอาหารมีพิวรีนสูง

อมร เปรมกมล*, พจน์ ศรีบุญลือ, ศรีน้อย มาศเกษม*, วัฒนะ ดิฐสถาพรเจริญ***

**ภาควิชาเวชศาสตร์ชุมชน, คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น, ** ภาควิชาชีวเคมี คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น, จังหวัดขอนแก่น*

ผู้ป่วยนิ่วไตในภาคอีสานมักจะมีอาการเรื้อรังหลายประการที่เรียกโดยรวมว่า "อาการอีสานรวมมิตร" ได้แก่ ปวดเส้นและกล้ามเนื้อ ปวดหลัง ปวดข้อ แน่นท้อง ปวดศีรษะ อ่อนเพลีย ร้อนที่สีข้าง ปัสสาวะแสบขัด ซึ่งอาการเหล่านี้จะกำเริบเมื่อกินอาหารพิวรีนสูง. ผู้วิจัยได้เคยรายงานว่าเมื่อให้ผู้ป่วยนิ่วไตที่มีเม็ดเลือดขาวในปัสสาวะดื่มชาชงหญ้าหนวดแมวติดต่อกันเป็นเวลานาน สามารถลดอาการเหล่านี้บางอาการรวมทั้งลดขนาดของนิ่วไตได้. วัตถุประสงค์ของการศึกษานี้เพื่อเปรียบเทียบสัมฤทธิผลของการรักษาผู้ป่วยอีสานรวมมิตรที่พบหรือไม่พบเม็ดเลือดขาวในปัสสาวะด้วยหญ้าหนวดแมวหรือหญ้าหนวดแมวบวกด้วยยาต้านจุลชีพ โดยดำเนินการวิจัยเชิงทดลองแบบสุ่มไม่ให้ผู้วัดและผู้ถูกวัดทราบว่าตนได้รับยาตัวใด ในพื้นที่ ๑๕ หมู่บ้านชนบทในจังหวัดขอนแก่น ในช่วงเดือนกุมภาพันธ์ ๒๕๔๗ ถึงกรกฎาคม ๒๕๔๘. ผู้ป่วยอีสานรวมมิตรที่เข้าร่วมโครงการ ๒๐๕ ราย แต่สามารถติดตามผลได้เพียง ๑๕๓ ราย (๗๕ รายไม่พบ และ ๑๑๘ รายพบเม็ดเลือดขาว) แบ่งผู้ป่วยแบบสุ่มเป็น ๔ กลุ่ม ได้แก่: ก๑ (๓๕ ราย), ก๒ (๓๖ ราย), ก๓ (๖๐ ราย) และ ก๔ (๕๘ ราย). กลุ่ม ก๑ ได้ยาหลอก, ก๒ ได้ผงสกัดของหญ้าหนวดแมว (๑ หลอด เทียบเท่า หญ้าหนวดแมวแห้ง ๑.๗ กรัม), ก๓ ได้ยานอร์ฟลอกซาซิน ๔๐๐ มิลลิกรัม, และ ก๔ ได้ยาผงสกัดของหญ้าหนวดแมวบวกด้วยยานอร์ฟลอกซาซิน. ยาทุกตัวถูกบรรจุในหลอดลักษณะเหมือนกัน. ยาสำหรับแต่ละหมายเลขในแต่ละกลุ่มย่อยจะจัดไว้ล่วงหน้าตามการสุ่มและนำรหัสไปเก็บซ่อนไว้จนถึงขั้นตอนการวิเคราะห์ข้อมูลจึงเปิดออก ทุกกลุ่มเต็มใจงดอาหารพิวรีนสูงในช่วง ๒ สัปดาห์ของการวิจัย. เมื่อใช้เกณฑ์การรักษาประสบผลสำเร็จคือคะแนนความเจ็บปวดของแต่ละอาการที่กำลังกำเริบอยู่ก่อนเข้าสู่การทดลองลดลง ≥ ร้อยละ ๕๐ ในผู้ป่วย ≥ ร้อยละ ๕๐.

ผลการทดลองแสดงว่าทั้ง ๔ กลุ่มกินอาหารพิวรีนสูงลดลงกว่าร้อยละ ๕๐. ผลต่อการลดของความรุนแรงของทุกอาการที่มีในตอนเริ่มต้นผ่านเกณฑ์ที่ตั้งไว้ทุก ๆ อาการในทุกกลุ่ม ภายใน ๒ สัปดาห์ (ค่าพี < ๐.๐๐๑, Friedman test) โดยไม่พบความแตกต่างในระหว่างกลุ่ม ไม่ว่าจะเป็นกลุ่มที่ได้ยาหลอก ผงสกัดของหญ้าหนวดแมว ยานอร์ฟลอกซาซิน หรือได้ยาผงสกัดของหญ้าหนวดแมวบวกด้วยยานอร์ฟลอกซาซิน แต่หากดูจำนวนอาการที่กำเริบขึ้นใหม่เมื่อเข้าโครงการเปรียบเทียบระหว่างสัปดาห์ที่ ๑ กับสัปดาห์ที่ ๒พบว่าเฉพาะกลุ่ม ก๑ (ยาหลอก) ที่จำนวนอาการไม่ลดลง ในขณะที่กลุ่ม ก๒, ก๓, ก๔ นั้นมีการลดลงอย่างมีนัยสำคัญทางสถิติ (ค่าพี <0.05, ไค-สแควร์ เพียร์สัน).

สรุปการศึกษาว่าการงดอาหารพิวรีนสูงสามารถลดความรุนแรงของอาการต่าง ๆ ของผู้ป่วยอีสานรวมมิตรในทุกกลุ่มที่ศึกษาได้อย่างมีนัยสำคัญทางสถิติ เมื่อประเมินใน ๒ สัปดาห์ แต่กลุ่มที่ได้หญ้าหนวดแมวและ/หรือยานอร์ฟลอกซาซินจะมีอาการอื่น ๆ หายไปด้วยในสัปดาห์ที่ ๒.

คำสำคัญ : **จุกแน่นท้อง, อ่อนเพลีย, ปวดกล้ามเนื้อและเส้นเอ็น, นอร์ฟลอกซาซิน, หญ้าหนวดแมว, อาหารพิวรีนสูง, นิ่วไต**