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Efficacy of Japanese-Oriental (Kampoh) Medicine applied to elderly patients with asymptomatic bacteriuria

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Abstract

We tried to evaluate the efficacy of Japanese-Oriental (Kampoh) Medicine (JOM) in 24 elderly patients who had asymptomatic bacteriuria. We divided the individuals into 4 groups, one control group and three trial groups, differentiating and prescribing each individual based on 'sho' criteria. The three groups had 3 different JOM decoction respectively ; Chorei-to-go-shimotsu-to (Zhi-Ling-Tang-He-Si-Wu-Tang), Seishin-rensi-in (Qing-Xin-Lian-Zi-Yin), and Ryutan-shakan-to (Long-Dan-Xie-Gan-Tang) for 28 days. Comparing trial and control groups before and after the medication trial we found these statistically significant facts : 1) increased secretory IgA in urine 2) increased blastgenesis of lymphocytes before taking mitogens 3) decreased blastgenesis of lymphocytes induced by pokeweed mitogen. There were also trends toward : 4) increased ease in urination 5) decreased sense of general fatigue 6) decrease in headaches. We think it important for the elderly individual with asymptomatic bacteriuria to be treated with JOM for better health care.

Key words asymptomatic bacteriuria, Urinary Tract Infection, urinary secretory IgA, Japanese-Oriental (Kampoh) Medicine, sho criteria.

Abbreviations UTI, Urinary Tract Infection ; JOM, Japanese-Oriental (Kampoh) Medicine ; PWM, pokeweed mitogen ; Con-A, concanavalin A ; PHA, phytohemagglutinin ; Chorei-to-go-shimotsu-to (Zhi-Ling-Tang-He-Si-Wu-Tang), 猪苓湯合四物湯 ; Seishin-rensi-in (Qing-Xin-Lian Zi-Yin), 清心蓮子飲 ; Ryutan-shakan-to (Long-Dan-Xie-Gan-Tang), 竜胆瀉肝湯.

Introduction

Bacteriuria is much more common in the geriatric population than in younger adults. At least 20 % of women and 10 % of men over 65 years of age have bacteriuria.[1)] According to some studies, the prevalence of bacteriuria among the elderly also rises substantially with increasing age.[2,3)] In these cases, it has been discussed for a long time whether or not to use medicine in treating patients.[1)] Most of the non-treated cases have not developed Urinary Tract Infection (UTI), but recently, in some cases, it is well known that severe UTI or renal failure has developed.[5)] Therefore, it has been thought that asymptomatic bacteriuria is subject to medication. Antimicrobial Therapy is a popular treatment for bacteriuria.[6)] In this study, we tried evaluate JOM effectiveness against asymptomatic bacteriuria. We have studied JOM in various basal and clinical research in Japan ; for chronic renal failure and Rhubarb Therapy,[7)] hemodynamics and Keishi-bukuryo-gan,[8)] Nephrosis and Saikosaponin-d,[9)] lipid metabolism and Hachimi-Gan[10)] and granulocyte-macrophage colony-stimulating factor and Ninjin-yoei-to,[11)] *etc.* However, the interaction between the host and JOM in elderly patients with asymptomatic bacteriuria has not been well investigated. In this study, we intended

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to evaluate the efficacy of JOM for hospitalized elderly people with asymptomatic bacteriuria.

Patients and Methods

Patients : There were 24 patients (mean age 85.8 years, range 70-99 years) with asymptomatic bacteriuria. These were patients with a history of continuous bacteriuria for 6 months or patients with 3 or more months bacteriuria within a 6 month period. Patients with asymptomatic bacteriuria had a positive urine culture with more than 10^5 CFU/ml of organisms and no acute symptoms referable to the urinary tracts. Eighteen patients with asymptomatic bacteriuria had no evidence of significant anatomical or functional abnormalities as defined by intravenous pyelogram, cystourethrogram, and echogram. Three patients had a cyst of the kidney and another three patients had mild benign prostatic hyperplasia (Table I). These patients with mild benign prostatic hyperplasia were included in the control group. Patients with Rheumatoid Arthritis in the study remained in an inactive stage of Rheumatoid Arthritis. And Chronic Bronchitis patients all remained at an inactive stage of Chronic Bronchitis throughout the trial period.

Trial design : The trial ran from October 20 to December 7 in 1991. We divided the individuals into 4 groups, one control group and three trial groups, differentiating and prescribing each individual after 'Sho' criteria. (Sho [12] is the name given to the traditional concept where the complex signs and symptoms of each patient are evaluated and then prescribed.) The three groups took 3 different JOM decoction respectively ; Chorei-to-go-shimotsu-to (Zhi-Ling-Tang-He-Si-Wu-Tang), Seishin-rensi-in (Qing-Xin-Lian-Zi-Yin), and Ryutan-shakan-to (Long-Dan-Xie-Gan-Tang) for 28 days. Then we compared and evaluated the effects of these formulae on each group in terms of immunological changes and complaints. The control group took the same volume of boiled water.

Preparation of JOM (Chorei-to-go-shimotsu-to, Seishin-rensi-in, Ryutan-shakan-to) : Three different JOMs were prepared in a 240 ml decoction (40°C); the ingredients were gently boiled in 600ml of water for 40 minutes just before administration (Table II). Ingredients used were purchased from Uchida (Tokyo, Japan). There were three medication times per day, two hours after meals.

Specimen collection in urine : Urine specimens were collected at 10 A.M. by catheterization.

Quantification of urinay secretory IgA (s-IgA): The amount of s-IgA in the urine was measured by EIA method (M.B.L. co.). The lower detection limit of this method was 0.07 μg/ml urine and creatinine was determined at the same time.

Mesurement of other laboratory examinations: We examined serum type IgA, IgM and IgG ; liver function (glutamic oxaloacetic transaminase, glutamate pyruvate transaminase, lactate dehy-

Table I Characterisics of subjects

Number (male/female)	24 (8/16)
Age	
Mean±S.E.	85.8±2.3
Range	(70−99)

Predisposition			
Hypertension	5	Benign Prostatic Hyperplasia	3
Osteoporosis	5	Valvular Disease of Heart	3
Diabetes Mellitus	4	Chronic Bronchitis	3
Rheumatoid Arthritis	4	Cerebral Infarction	3
Cyst of the Kidney	3	Old Myocardial Infarction	2
Dementia	3		

Table II Contents of Japamese-Oriental Medicinal formulae

A. Chorei-to-go-shimotsu-to		
Chorei (猪苓)	*Polyporus umbellatus Fries*	3.0 g
Bukuryo (茯苓)	*Poria cocos Wolf*	3.0 g
Kasseki (滑石)	*Talcum depuratum*	3.0 g
Takusha (沢瀉)	*Alisma orientale Juzepc.*	3.0 g
Akyo (阿膠)	*Equus asinus L.*	3.0 g
Toki (当帰)	*Angelica acutiloba Kitagawa*	3.0 g
Shakuyaku (芍薬)	*Paeonia lactiflora Pall.*	3.0 g
Senkyu (川芎)	*Cnidium officinale Makino*	3.0 g
Jiou (地黄)	*Rehmannia glutinosa Lib., var. pupurea Mak.*	3.0 g
B. Seishin rensi in		
Renniku (蓮肉)	*Nelumbo nicifera Gaertn.*	4.0 g
Bakumondo (麦門冬)	*Ophiopogon japonicus Ker-Gawl.*	4.0 g
Bukuryo (茯苓)	*Poria cocos Wolf*	4.0 g
Ninjin (人参)	*Panax ginseng C.A. Mey.*	3.0 g
Shazensi (車前子)	*Plantago asiatica L.*	3.0 g
Ogon (黄芩)	*Scutellaria baicalensis Georgi*	3.0 g
Ogi (黄耆)	*Astragalus membmaceus Bge.*	2.0 g
Jikkopi (地骨皮)	*Lycium chinense Mill.*	2.0 g
Kanzo (甘草)	*Glycyrrhiza glabra L. var. glandulifer Reg. et Herd, G. uralensis Fisch.*	1.5 g
C. Ryutan-shakan-to		
Shazensi (車前子)	*Plantago asiatica L.*	5.0 g
Ogon (黄芩)	*Scutellaria baicalensis Georgi*	5.0 g
Takusha (沢瀉)	*Alisma orientale Juzepc.*	5.0 g
Mokutu (木通)	*Akebia quinata Decaisne.*	5.0 g
Jiou (地黄)	*Rehmannia glutinosa Lib., var. purpurea Mak.*	5.0 g
Toki (当帰)	*Angelica acutiloba Kitagawa*	5.0 g
Sanshishi (山梔子)	*Gardenia jasminoides Ellis*	1.5 g
Kanzo (甘草)	*Glycyrrhiza glabra L. var. glanduifera Reg. et Herd, G. uralensis Fisch.*	1.5 g
Ryutan (竜胆)	*Gentiana scabra Bunge*	1.5 g

drogenase, alkaline phosphatase, γ-glutamyl transpeptidase); kidney function (blood urea nitrogen, creatinine); total cholesterol, high density lipoproteins cholesterol and triglyceride; total protein and C-reactive protein before, during and after medication. We asked B.M.L. co. to perform the measurement of lymphocyte blastgenesis and lymphocyte subpopulations.

Complaints check: The number of clinical questions asked were 204. The questions were graded on a scale from 0 to 4. We gave a complaint check to the 24 patients twice during the experiment, before medication and 3 weeks after medication. We defined a change of 2 on the scale to be significant.

Data Analysis: The data were analyzed using the Wilcoxon statistic test for non-parametric populations. Statistical significance was defined at the $p<0.05$ level. All data were given as mean $\pm$S.E.

Results and Discussion

Table I shows the characteristics of subjects.

We divided the individuals into 4 groups (Table III), one control group and three trial groups, differentiating and prescribing each individual after 'sho' criteria. Table IV illustrates 'sho' criteria for these JOM. Fig. 1 shows the change in s-IgA levels in the urine of subjects with asymptomatic bacteriuria. The s-IgA levels after administration were significantly increased compared with pre-adminstration. A potential protecive function of urinary s-IgA is indicated by in vitro experiments. These demonstrate that it may prevent the adhesion of bacteria to uroepithelial cells.[13] In vivo studies have repeatedly shown that s-IgA levels rise in response to bacterial infection ;[14-17] however, this is the first report indicating increased urinary s-IgA levels by JOM administration. Fig. 2 shows cpm counts of lymphocyte blastgenesis before taking mitogen (basal cpm count of lymphocytes). Cpm counts after administration were higher compared to counts before administration. It is well known that infections or the taking of immuno-activators increases basal cpm counts of lymphocytes.

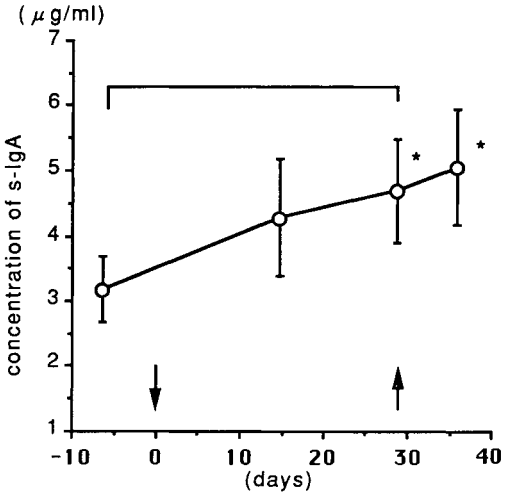

Fig. 1 Medicational effect on s-IgA
(n=18), *: ($p<0.05$), ○—○ : s-IgA
↓: start of medication ↑: end of medication.

Table III Clinical Characteristics of Patient Groups

Charactaristics	Group A	Group B	Group C	Group D
Number	6	6	6	6
Age	89.0±2.3	85.3±2.0	84.7±3.3	84.2±2.9
Sex (male/female)	(1/5)	(1/5)	(2/4)	(4/2)
CRP (+)	(1/6)	(1/6)	(1/6)	(0/6)
Fever	(0/6)	(0/6)	(0/6)	(0/6)
Proteinuria	(1/6)	(1/6)	(0/6)	(1/6)
Serum creatinine	1.28±0.13	1.09±0.86	1.45±0.19	1.02±0.17

Group A ; Chorei-to-go-shimotsu-to, Group B ; Seishin-rensi-in,
Group C ; Ryutan-shakan-to, Group D ; control, mean±S.E.

Table IV Sho criteria

Group A	Chorei-to-go-shimotsu-to	6 cases
	thirsty, sleeplessness, dry skin, pale face, hotness of hands and feet	
Group B	Seishin-rensi-in	6 cases
	bitterness in oral cavity, weak stomach, chills, depressive state, shoulder stiffness, epigastric discomfort, weak abdominal tension, palpable of aortic beat in upper navel	
Group C	Ryutan-shakan-to	6 cases
	brown skin color, wetness of hands and feet, irritability, tension of bilateral abdominal rectus muscle	

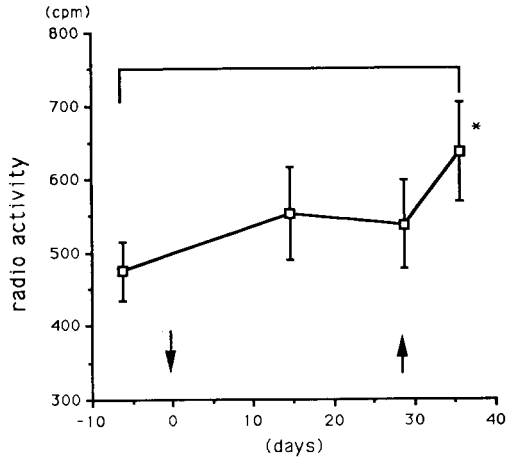

Fig. 2 Medicational effect on blastgenesis (basal control)
(n=18), *: ($p<0.05$), □—□ : basal control
↓: start of medication ↑: end of medication.

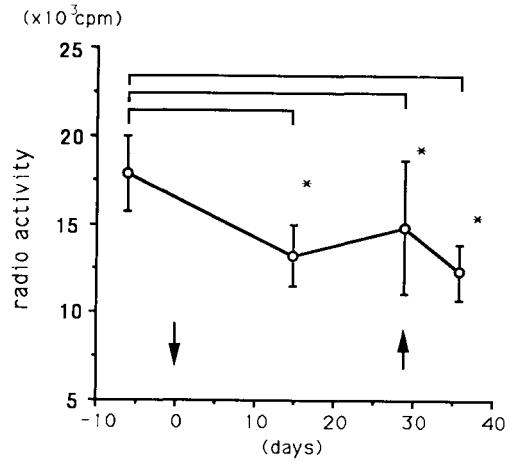

Fig. 3 Medicational effect on blastgenesis (PWM)
(n=18), *: ($p<0.05$), ○—○ : PWM
↓: start of medication ↑: end of medication.

Here it was suggested that JOM may activate peripheral lymphocytes. Fig. 3 shows cpm counts of pokeweed mitogen (PWM) stimulation on lymphocyte blastgenesis. Cpm counts after administration were less than before administration. However, cpm counts of concanavalin A (Con-A) and phytohemagglutinin (PHA) didn't have a significant change due to administration. The discrepancy between the three mitogens is not clear.

Fig. 4 shows that CD3, CD4 and CD8 had no significant change. Recent studies show the number of T-cells in peripheral blood decreases with age. Ordinarily, the number of granulocytes, monocytes and B-cells does not change due to aging. In the T-cell subset, decreases of CD8 positive cells are more dramatic than that of CD4 positive cell,[18] and there is found not only a quantitative change but also a qualitative one. It may be that B-cell function changes depend upon T-cell changes. Among CD8 positive cells, CD4 positive cells and B-cells the results of cell proliferation activity due to phorbol myristate acetate and ionomycin stimulation show that the activity of CD8 positive cells is the lowest and that of CD4 positive cells the second lowest.[19] Because these results come from different methods, it is difficult to compare our findings with them, but it is well known that Con-A and PHA do stimulate T-cells and that PWM stimulate both T- and B-cells. If B-cells potentially have a dominant influence in blastgenesis, cpm counts would be increased. The reason is not clear, but B-cells may be influenced by JOM.

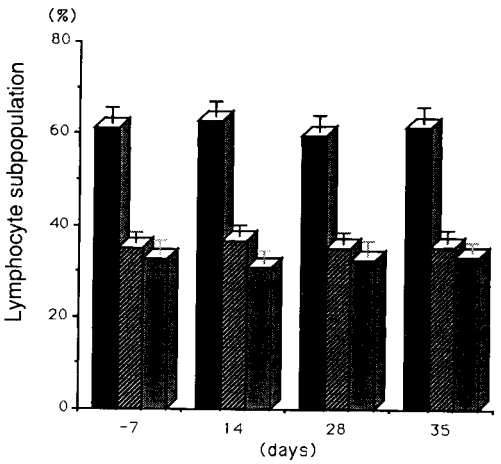

Fig. 4 Medicational effect on lymphocyte subpopulations (CD3, CD4, CD8)
(n=18) ■ CD3, ▨ CD4, ▩ CD8
Horizontal axis shows days in which zero is the start of medication.

The amount of bacteria and bacteria species had no change before and after medication (Table V). If a subject specimen had two or more bacteria, each bacterium was counted respectively.

Table V Culture of Asymptomatic Bacteriuria

Bacteria		Cases Administration Before	After
Gram (+)	*Staphylococcus*	6	6
	E. faecalis	3	3
	Subtotal	9	9
Gram (−)	*E.coli*	3	3
	Citrobacter	2	2
	Klebsiella	8	8
	Proteus	4	4
	Enterobacter	2	2
	Subtotal	23	23
	Total	32	32

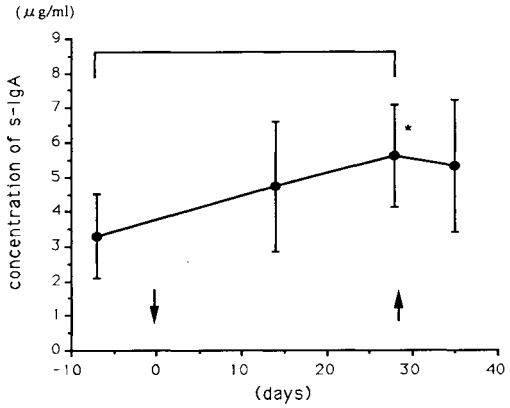

Fig. 5 Medicational effect on s-IgA (Seisin-rensi-in)
(n=18), *: ($p<0.05$), ●—● : s-IgA
↓: start of medication ↑: end of medication.

Two thirds of bacteria in urine belong to *Enterobacteria, Staphylococcus, Klebsiella* and *Proteus*. These were the major bacteria found in this study, and these bacteria are common in chronic UTI.

We analyzed significant changes for each JOM respectively. Fig. 5 shows that Group B (Seishin-rensi-in) had significantly increased s-IgA in their urine. The other laboratory data did not show significant change. (Data not shown).

Complaint checks were performed before and during administration. The improvement of complaints is shown in Table VI. Major improvements include: 1)inceased ease in urination, 2) decreased sense of general fatigue, 3) decreased headache and 4) decreased feeling of depression. Thus, it appears that complaints can be reduced by JOM administration. These complaints are usually found in elderly persons.

Therefore, JOM administration may prove beneficial to elderly patients. In this study, increased s-IgA, which concerns local immunity to UTI, was found. Also, the basal control of lymphocyte blastgenesis was increased. It is favourable that JOM activates the immune system. We think it is important for the elderly individual with asymptomatic bacteriuria to be treated with JOM for their better health care. We have researched the effects of JOM as applied to elderly patients with asymptomatic bacteriuria. For our next approach, we must study long- term effects of how JOM specifically acts within the body on other diseases of elderly patients.

Table VI Improvement of complaints

	Group A	Group B	Group C	Group D
1) Increased ease in urination	1/3	5/6	1/3	0/2
2) General fatigue	3/5	4/5	1/2	0/3
3) Feeling of unpleasantness	1/3	3/4	2/3	0/2
4) Feeling of irritation	1/2	2/3	0/1	0/0
5) Feeling of depression	1/3	4/5	1/2	0/2
6) Faded afternoon somnolence	1/2	1/3	1/1	0/3
7) Headache	0/3	3/4	1/3	0/2
8) Itching	1/2	2/3	1/2	0/2

The number of patients with improvement/The number of patients with complaint.
Group A ; Chorei-to-go-shimotsu-to Group B ; Seishin-rensi-in
Group C ; Rutan-shakan-to Group D ; control

和文抄録

無症候性細菌尿を有する高齢者24名に対して和漢薬方剤を投与し，その効果について血液生化学的，免疫学的，および自覚症状の各分野について検討した。対象患者を随証的に方剤投与群3グループ各6名とコントロールグループ6名に分類した。方剤投与グループには，猪苓湯合四物湯，清心蓮子飲，竜胆瀉肝湯の3方剤をそれぞれ湯液で28日間投与した。方剤の投与前後における種々のパラメーターのうちで有意な変化を示したものは，1.尿中分泌型IgAの上昇 2.リンパ球幼弱化試験のマイトジェン投与前の基礎値の上昇 3. PWMによるリンパ球幼弱化試験の活性低下を認めた。そして自覚症状の変化として 4.1回に出る尿が良く出るようになった，5.倦怠感が減少した 6.頭痛が起こりにくくなった，等の改善を認めた。この研究で高齢者の無症候性細菌尿患者に対して和漢薬方剤を投与することで，下部尿路感染症の防御機構のひとつである尿中分泌型IgAを上昇させ，加えて高齢者のQOLの向上にも有用であることが明らかになった。

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