2011. Vol.32. No.6. *122-130*
The Journal of Korean Oriental Medicine

Case Report

Effects of Herbal treatment for In-patients with Mild Fever: Retrospective Clinical Study

Sun-ju Lee[1], In-sik Han[1], Hyun-suk Oh[1], Dong-jin Lee[1], Jeung-won Yoon[3], Ga-young Choi[1], Sun-gi Hong[2], Won-chul Lee[1], Seung-ho Sun[1]

[1]Department of Oriental Internal Medicine, Oriental Hospital of Sangji University
[2]Department of Sasang Constitution, Oriental Hospital of Sangji University
[3]East-West Cancer Center, Dunsan Oriental Hospital of Daejeon University

Objectives: This study was designed to investigate the effect of herbal extract medicines for inpatients with fever symptoms in an oriental medicine hospital.
Methods: Medical records of inpatients who experienced over 38℃ of fever from July 2010 to August 2011 has been requested with deleted personal identifiable information. The requested data were analyzed by patients' general characteristics, administrated western/herbal medicines, and changes in the body temperature of four administration groups (group 1, herbal extract medicine only; group 2, western medication(antibiotics/antipyretics) only; group 3, combination of herbal extract medicine and western medication; group 4, no medication control). The SPSS 19.0 was used for statistical analysis and p-value of less than 0.05 was regarded significant.
Results: The body temperature has significantly dropped over time in the herbal extract medicine only group ($p< 0.001$) along with the antibiotics/antipyretics only group. When both treatments were combined, stronger antipyretic effect was shown compared to the sole treatment of herbal extract medicine or antibiotics/antipyretics.
Conclusion: The use of herbal extract medicines may be effective in alleviation of fever.

Key Words : fever, herbal extract, antibiotics, antipyretics, combined medication

Introduction

Fever is a condition of raised body temperature over its normal range of 37.2℃[1)]. In western medicine, cause of fever and the diagnosis of the diseases are determined using various tests, then treated accordingly using antibiotics, antipyretics or external cooling methods[2)]. Antibiotics are generally not recommended before a confirmed diagnosis even when the infection is suspected. Preventive administration of antibiotics can lead to risk of clinical misjudgment and cause serious side effects[3)]. Inpatients are more likely to develop fever from compromised immune system caused by long term hospitalization, change of oral flora, and many invasive procedures[4)]. Therefore the antipyretics are also refrained from usage when the fever has not yet been confirmed or is below 38℃, as it can weaken the body resistance[1)]. For oriental medicine hospitals, it is difficult to run a blood lab or bacterial culture right away and requires a fast acting alternative without the side effects.

· Received : 21 October 2011 · Revised : 9 November 2011 · Accepted : 9 November 2011
· Correspondence to : Seung-ho Sun
Department of Oriental Internal Medicine, Oriental Hospital of Sangji University,
283, Woosan-dong, Wonju-si, Kangwon-do, 220-955, South Korea
Tel : +82-33-741-9209, Fax : +82-33-741-9141, Email : sunguy2001@hanmail.net

There are reports of several oriental medicine treatments for fever and number of literature reviews[5-8] and clinical researches[4,9-14]) support the antipyretic effect of these treatments.

In this study, effects of various herbal extract medicines were compared with western medication of antibiotics or antipyretics for mild fever cases by reviewing the medical records retrospectively.

Materials and Methods

1. Subjects and methods

After the approval of the study protocol by the Institutional Review Board (IRB) of oriental medicine hospital of Sangji university, medical records from July 2010 to August 2011, according to inclusion and exclusion criteria, were requested through the medical record administrator. The requested data, coded in excel file without the personal identifiable information including the patient name, address, telephone number, social security number, and hospital registration number was provided for extraction and investigation. The received data was then further analyzed by gender, age, admission diagnosis, types of conventional/herbal medicines used for fever, dosing time, and the changes in body temperature after treatment.

1) Inclusion criteria

(1) Patients whose body temperature rose over 38℃ during the hospitalization period according to the medical records.

(2) The medical records must include the dosing time and follow up of temperature changes after the administration.

2) Exclusion criteria

Cases of transfer to other hospitals within the 6 hour window after drug administration due to emergency conditions such as altered state of consciousness or acute cerebrovascular attack and relapse were excluded.

Of the selected 79 fever incident cases that have met the inclusive criteria, 6 cases were excluded and total 73 cases were investigated for this study.

2. Assessment methods

1) General characteristics

The selected cases were analyzed by patients' gender, age, and admission diagnosis.

2) Types of medication

The types and dosing frequency of herbal extract medicines, antibiotics, antipyretics, and their combinations were investigated.

3) Comparison of body temperature changes between groups

The selected cases were divided into four groups; group 1, herbal extract medicine only; group 2, wetern medication(antibiotics/antipyretics) only; group 3, combination of herbal extract medicine and wetern medication; group 4, no medication control. The body temperatures of patients were recorded every 2, 4 and 6 hours after the administration, as the each dosing times were different from another. The changes in body temperature over time up to 6 hours were followed and compared among groups.

3. Statistical analysis

The frequency analysis on patients' gender, age, disease types, and kinds of herbal extract medicines and antibiotics or antipyretics used was performed. The nominal variable is shown as the frequency and percentage (n, %) and the continuous variable is presented as mean and standard deviation (Mean±SD). The antipyretic effect and the changes of body temperature in every 2, 4 and 6 hours among groups were analyzed by Repeated Measures Analysis of Variance (RM ANOVA). Kruskal Wallis test was used to compare

the differences in body temperature decrease 6 hours after the administration depending on medication and disease types. The SPSS 19.0 was used for statistical analysis and p-value of less than 0.05 was regarded statistically significant.

Results

1. General characteristics

The total number of respondents was 2,203, composed of 51.1% and 48.9% men and women, respectively. The average age of both men and women was 39 (ranging from 18 to 64). The occupation was significantly different between the two genders, especially higher for physical work among men but for homemakers in women (Table 1).

2. Interventions

Various types of herbal extract medicines and antibiotics/antipyretics were used as the existing diseases and the accompanied symptoms differed for each patient. The herbal extract medicines were used in 61 cases total; herbal treatment only group (52 cases) and the combination group (9 cases). Yeongyo-paedok-san extraction was the most commonly prescribed extraction with 10 cases, followed by combined extraction of Mahaenggamseok-tang and Eunkyo-san given in 9 cases. The antibiotics/antipyretics were used in 18 cases total; western medication only group (9 cases) and the combination group (9 cases). Levofloxacin tablet, Micronomycin and Cefazolin sodium injection were each used in 4 cases, and Diclofenac sodium injection was used in 3 cases (Table 2).

3. Antipyretic effects of interventions

The 4 groups (Table 3, Fig. 1) had 52 cases of herbal extract medicines only, 9 cases of antibiotics/antipyretics, 9 combined cases of herbal extract medicines and antibiotics/antipyretics, and 3 cases of no medication control. In all 4 groups, significant temperature decrease was shown over time ($p<0.001$). Up until 4 hours into treatment, body temperature decrease was shown in all groups. During the 2 hour window between the second and fourth hour, the combination group has shown faster decrease compared to all other groups. Between the fourth and sixth hour window, increase in body temperature was observed in the control group and no change in temperature was observed in western medication only group. For herbal extract medicine only group and the combination group, continued drop of body temperature was observed. However, no statistical significance was found in changes of temperature measured at every 2, 4, and 6 hours after administration between all groups ($p=0.068$). Overall, highest drop of temperature was

Table 1. Demographic Characteristics of Cases (n=73)

		n	%
sex	female	39	53.4
	male	34	46.6
age (mean±SD)		66.40	±16.02
Diagnosis	cerebrovascular disease	38	52.1
	internal disease	15	20.5
	musculoskeletal diseases	12	16.4
	Infectious diseases	5	6.8
	malignant neoplasms	3	4.1

SD : Standard Deviation

Table 2. List of Medications on Administration Groups

group*	Herbal extracts / antibiotics, antipyretics	n	%
1	Gamisoyosan	1	1.9
	Galgeuntang	1	1.9
	Galgeunhaegitang	1	1.9
	Galgeunhaegitang+Yeongyopaedoksan	1	1.9
	Geotonghwan	2	3.8
	Gumiganghwaltang	1	1.9
	Mahaenggamseoktang	6	11.5
	Mahaenggamseoktang+Yeongyopaedoksan	2	3.8
	Mahaenggamseoktang+Eunkyosan	8	15.4
	Mahaenggamseoktang+Hwangnyeonhaedoktang	2	3.8
	Mahwangbalpyotang	2	3.8
	Hyeongbangpaedoksan	2	3.8
	Socheongnyongtang	1	1.9
	Yeongyopaedoksan	8	15.4
	Hwangnyeonhaedoktang	2	3.8
	Yeongyopaedoksan+Hwangnyeonhaedoktang	2	3.8
	Eunkyosan	2	3.8
	Eunkyosan+Hwangnyeonhaedoktang	5	9.6
	Insampaedoksan	1	1.9
	Jaeumganghwatang	2	3.8
	total	52	100.0
2	levofloxacin tablet	2	22.2
	cefazolin sodium injection	1	11.1
	micronomycin sulfate injection	1	11.1
	micronomicin sulfate injection+cefazolin sodium injection	2	22.2
	diclofenac sodium injection	1	11.1
	ribostamycin sulfate+cefazolin sodium injection	1	11.1
	amoxicillin+clavulanate potassium 7:1 tablet	1	11.1
	total	9	100.0
3	Eunkyosan / levofloxacin tablet	1	11.1
	Yeongyopaedoksan+Eunkyosan / micronomicin sulfate injection+cefazolin sodium injection	1	11.1
	Mahaenggamseoktang+Yeongyopaedoksan / levofloxacin tablet	1	11.1
	Maengmundongtang / acetaminophen tablet	1	11.1
	Mahaenggamseoktang+Eunkyosan / micronomicin sulfate injection+cefazolin sodium injection	1	11.1
	Hwangnyeonhaedoktang / cefazolin sodium injection	1	11.1
	Mahaenggamseoktang+Yeongyopaedoksan / ribostamycin sulfate injection+acetaminophen tablet	1	11.1
	Yeongyopaedoksan / diclofenac sodium injection	2	22.2
	total	9	100.0
4	no medication	3	100.0
	total	3	100.0
	Great Total	73	

*group 1 : only herbal extract medicine
group 2 : only western medicine
group 3 : combination (both herbal and western medicine)
group 4 : control group

Table 3. Changes of Body Temperature after Administration and Decrease of Body Temperature after 6 Hours

Administration group	n	body temperature after administration				P value*	decrease	P value†
		0	2hrs	4hrs	6hrs			
Herbal extracts	52	38.5±0.5	38.2±0.5	38.0±0.5	37.8±0.5	0.068	0.7±0.6	0.679
Western medicine	9	38.9±0.7	38.5±0.7	38.4±1.2	38.4±1.1		0.5±1.3	
Both herbal medicine and Western medicine	9	38.7±0.7	38.4±1.1	37.7±0.8	37.6±0.8		1.1±1.4	
Control group	3	38.3±0.2	38.1±0.2	37.8±0.3	37.9±0.2		0.3±0.2	
Total	73	38.5±0.5	38.2±0.6	38.0±0.6	37.8±0.7		0.7±0.8	

The results of temperature are the mean±Standard Deviation.
Western medicine : Antibiotics or antipyretics
* P value was evaluated by Repeated Measures Analysis of Variance (Changes of the body temperature among groups by administration)
† P value was evaluated by Kruskal Wallis test (Decrease : Body temperature before administration - Body temperature when 6 hour)

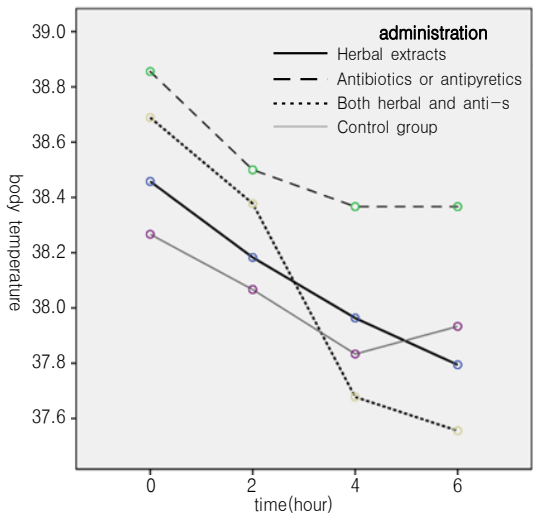

Fig. 1. Changes of the Body Temperature among Groups by Administration

seen in the combination group with 1.1±1.4℃ decrease. herbal extract medicine only group was next in line with 0.7±0.6℃ decrease followed by western medication only group and the control group. There was no statistical significance among groups in decrease of body temperature (p=0.679). Six hours into treatment, lowest average body temperature was shown in the order of combination group, herbal extract medicine only group, western medication only group, and the control group. The average body temperature remained over 37.5℃ in all four groups.

Discussion

Fever is a condition of elevated body temperature above the normal range of 35.8~37.2℃ due to an altered temperature regulation control system located in hypothalamus[15]. Fever is generally divided into three states of mild fever(37.2~37.9℃), average-grade fever(38~38.9℃), and high fever(over 39℃)[16]. The range of so called 'normal' body temperature as an oral temperature is 37℃(36~37.4℃), axillary temperature is 36.5℃, and rectal(tympanic membrane) temperature is 37.5℃. Pulmonary artery, urinary bladder, rectum,

mouth, ear-based and axillary temperatures are sites used for temperature measurement, though not all of them common. As for the accuracy of the measurement, axillary temperature is reported to be relatively inaccurate and bladder, mouth, rectum, ear-based measurements are more ideal for correct measurements[17].

If a patient has a fever, the body temperature is checked once or twice to estimate the degree and type of the fever. Thereafter, researchers also find out the cause and diagnose the disease through examinations such as blood, urine, stool, sputum and X-ray in addition to other physical examinations.

Fever can be caused by infection, tissue lesions, tumor, immune disease, acute metabolic disorders and other diseases affecting the body's temperature regulating system. Sometimes it is accompanied by other symptoms such as headache, whole body myalgia, knee pain, weakness, dysphoria, chills, herpes labialis, confusion and spasm.

In oriental medicine, fever is differentiated into several categories; Aversion to cold with fever (惡寒發熱), High fever (壯熱), Tidal fever (潮熱), Alternating chills and fever (寒熱往來), Vexing heat (煩熱), Mild fever (微熱), Bone-steaming fever (骨蒸熱)[18]. In 'Treatise on cold pathogenic diseases' (傷寒論), fever is classified into three meridian patterns of Yangming, Taiyang and Shaoyang. In 'Warm disease theory' (溫病學), different types of fever are discussed in relation to seasons and other external/internal conditions. According to the theory, fever is caused by External pathogenic attack (外感) or Internal injury (內傷). External pathogenic attack (外感) usually features a high fever and an acute, short-term progress compared to the Internal injury (內傷) induced fever. Treatment principles of Dispelling wind and dissipating cold (祛風散寒), Releasing the exterior with pungent-warm (辛溫解表) are used to treat fever caused by External pathogenic attack (外感) and Tonifying and nourishing yin fluids (滋養陰液), Pacifying liver and draining fire downward (淸肝降火) methods are used to treat fever caused by Internal injury(內傷).

In western medicine, external cooling, antipyretic drugs (aspirin, acetaminophen etc), NSAIDs (Non-steroidal anti-inflammatory drugs) and antibiotics are commonly used in treating fever[2]. For mild or average-grade fever aggressive treatment is rarely given as it is part of a normal phenomenon to protect our bodily functions. Preventive antibiotics are neither recommended due to the drug side effects and risk of clinical misjudgment. However, high unremitting fevers can be fatal and special attention is needed for such cases[20].

Several studies report efficacy of oriental medicine for treatment of fever. A documentary review was done on meridians and acupoints for fever decrease[5]. Administration of Hwangnyeonhaedok-tang (黃連解毒湯), and Onsungouhyoulbang (溫性瘀血方) per oral or by using aqua-acupuncture was reported to have pain controlling, anti-inflammatory, and antipyretic effect[6]. Blood-letting on Sybsunhyul (十宣穴) and Taechu-hyul (大椎穴) proved to be effective for emergency febrile conditions8). Research has been conducted on single herbs and herbal formulas including *CimicifugaeRhizoma* (升麻), Darwon-eum (達源飮), Kumbaekjeopi-hwan (芍栢樗皮丸), Chunglijagam-tang kami (淸離滋坎湯加味), Manhyoungja-san (蔓荊子散), and Bangpunghaedok-tang (防風解毒湯)[4,9-13]. Use of Bojoongikki-tang (補中益氣湯) for patients suffering from Internal injury induced fever (內傷發熱) types showed valid efficacy as well[14].

In this study, retrospective investigation was conducted referring to medical records in order to compare the decline of body temperature after taking herbal extract medicines. Regarding the treatments received, other therapies such as cupping and blood-letting on Sybsunhyul(十宣穴) may have acted as variable factors. However, the therapies have always been a part of routine clinical practice in the hospital and the clinical effects of cupping and blood-letting on acupoints are quite different from that of herbal medication in the aspect of sustainability. Instead, we performed longer follow up of the patients to prevent variables from interfering the study results.

In the study, number of female subjects was higher than male subjects and the average age was 66.4±16. Many of them were diagnosed with cerebrovascular diseases (52.1%) and internal diseases (20.5%) which are general diseases types of patients hospitalized in oriental medicine hospitals. With their compromised immunity and increased chances of infection, fever is one of the most commonly developed symptoms[19].

Yeongyopaedok-san (連翹敗毒散), Mahaenggamsuk-tang (麻杏甘石湯) and Eungyo-san (銀翹散) extracts were commonly used. According to studies of Park[21] and Han[22], Warm disease theory (溫病學) diagnosis and herbal formulas were found effective on the early stages of pneumonia and cerebrovascular disease followed by pneumonia.

All treatment groups showed significant decrease of body temperature over time, though no statistical significance was found in differences between groups including the control group. However, the control group has also received traditional therapies like cupping and blood-letting on Sybsunhyul (十宣穴) so it was hard to be considered a genuine control group. In medical records, body temperature was recorded up to 24 hours from the initial treatment. This study only followed up until 6 hours after treatment, as next line of treatments were given if the fever persisted more than 6 hours.

The graph (Fig. 1) shows that body temperature didn't decrease four hours after antibiotics or antipyretics were administered and body temperature elevated again in control group. On the other hand, the group of herbal medicine extracts showed constant body temperature decrease.

In case of herbal medicine extracts combined with antibiotics or antipyretics, body temperature sharply decreased from 2 to 4 hours after administration. It is found that the combination of both medications is much more effective in dealing with fever since body temperature decrement after 6 hours was the biggiest(1.1±1.4℃) as shown on the graph.

Tendency to use combined treatment for high grade fever over 38.5℃, and herbal extract medicines for 38.5℃ fever was seen.

Additional objective of the study was to compare regular herbal decoctions to herbal extract medicines. In clinical settings, herbal decoctions require longer time to prepare and by prescribing extractions considerable amount of time can be saved. As a result, the study proved herbal extract medicines to be effective for mild fever, especially when combined with western medication. Administering herbal extract medicines as a first line therapy for mild fever cases look optimistic for future applications.

There are some limitations in generalizing the study results as this was a retrospective study solely based on medical records. As mentioned above, difficulty in excluding variables like cupping or blood-letting therapies contributed to a vague control group. Disease types, age, and patients' initial body temperature were not equally set, and the number of patients differed in groups with use of varying kinds of herbal extract medicines. For some patients, temperature was checked every 4 hours and post-2 and 6 hour body temperatures were missing. In this case, the mean value between the hours was calculated and used contributing to high risk experimental errors. The statistical insignificance of the study is estimated to be caused by relatively large sample size of the herbal extract medicine only group. However, with its comparable antipyretic effects and synergistic effects with western medication shown in the study, further clinical studies are anticipated to reconfirm its value. Excess to related information such as direct cause of fever, accompanied symptoms and hematologic lab results were limited as the pre-coded patients files received from the medical records administration mainly included body temperatures in relation to the treatments provided. For future studies, differentiating herbal prescriptions according to the cause of fever and accompanying symptoms should be considered for more systemic results.

Conclusions

The combined therapy of herbal and western medicine has shown most efficacy in treating fever symptoms. However a single positive result within this study should be carefully interpreted. Further investigations and more systematic approaches to determine the antipyretic effects of herbal treatment are needed for future studies.

References

1. Kim JJ. Physiology. Seoul:Gomunsa. 1991:225-229.
2. Kim H, Oh TH, Jung SK, Lee HG. The Comparative Study between Oriental and western medicine on fever-focus on Sanghanron(傷寒論) and Onbyung hac (溫病學). The Journal of Korean Oriental Medicine. 1993;14(1):57-73.
3. Researcher of medical education. Family medicine. Seoul:Seoul national university press. 1990:85-87.
4. Kang KS, Roh GH, Ko CN, Kim YS, Lee KS. A Case Study on the High Fever of Patient Treated with Dalwonum. The Journal of Korean Oriental Internal Medicine. 2000;21(5):859-62.
5. Han SW, Kim EH, Park KH. A literature study about acupuncture point for fever. Thesis collection of Jehan oriental academy. 1999;4(1):250-261.
6. Kim KH, Kim SS. Study on analgesic, anti-inflammatory and antipyretic effects of Aqua-acupuncture and administration per orally of Whangryounhaedogtang (黃連解毒湯) and On-sungouhyoulbang (溫性瘀血方). The Journal of Korean Oriental Medicine. 1994;15(1):9-25.
7. Son DH, Lee YG, Kim YS, Bae HS, Lee KS, Joh KH. Effect of wet-cupping at Dachu(大椎, Dazhui)-point on fever in Patients with stroke. The Journal of Korean Oriental Medicine. 2001;22(3):119-128.
8. Kim JJ, Kim EJ, Lee SH, Rhee JW, Lee JH, Jung WS, et al. Antipyretic effect of blood-letting at the Sybsun-points on fever comparing with aspirin injection. The Journal of Korean Oriental Internal Medicine.2003;24(3)675-680.
9. Kwon IH, Kim NK, Chiang HC, Lim HJ, Kim JM. Antipyretic Effect of Rhizoma Cimicifugae in a Rat Model of LPS-induced Fever. The Journal of Korean Oriental Medicine. 2002;23 (4):32-44.
10. Yang SY, Lee KS, Song BK. The Effect of Kumbaekjeopihwan (芎栢樗皮丸) on the Febrifugal, Anti-inflammatory, Diuretic, and Antibacterial Activities. The Journal of Korean Oriental Medicine. 1985;6(2):88-97.
11. Hwang SI, Baek DG, Cho GI, Choi JY, Shin HS, Choi WJ, et al. A case study of fever of unknown origin with stroke patient. The Journal of Korean Oriental Internal Medicine. 2003;24(2):409-14.
12. Jang BS, Kim SS, Shin HD. An Experimental Study on the Analgesic and Sedation, Anti-inflammatory effect of Manhyoungjasan. The Journal of Korean Oriental Medicine. 1988;9(2): 59-70.
13. Jung WS, Moon SK, Cho KH, Kim YS, Bae HS, Lee KS. The transient antifebrile effect of Bangpunghaedok-Tang on the incipient Stage Fever. The KyungHee university medical journal. 1997;13(4):378-389.
14. Song KK, Seo YH, Jeon KO, Kwon EH, Moon JH, Choi HY, et al. Two cases of fever from deficiency of Qi. The Journal of Korean Oriental Internal Medicine. 2004;25(4-2):410-417.
15. The compilation committee of Harrison's principles of internal medicine. Harrison's principles of internal medicine. Seoul: Jungdam publishing group. 1997:81-87.
16. Kim HD, Yeo IY, Jeon WH, Park JM. A case report of fever of unknown origin(FUO). Korean

Journal of Oriental Internal Medicine. 2003;24 (3):700.

17. Jeon EJ, Lee HM, Cho SG, Kang HK, Kwak HW, Song JH, et al. Causes of fever in the ICU-A prospective, Cohort study. Korean Journal of Critical Care Medicine. 2008;23(1):13-17.
18. Lee BK. Diagnostics of Oriental medicine. Seoul: Sungbosa. 1997:159.
19. Jung WS, Moon SK, Cho KH, Kim YS, Bae HS, Lee KS. The transient antifebrile effect of Bangpunghaedok-Tang on the incipient Stage Fever. The KyungHee university medical journal. 1997;13(4):378-389.
20. Jefferey AG, Charles AD, Sheldon MW, Alterations in body temperature. In: Kurt JI, Eugene B, Jean DW, Joseph BM, Anthony SF, Dennis LK, et al. Harrison's principles of internal medicine. 13th ed. New York:McGraw-Hill. 1994:81-90.
21. Park JY, Go HY, Jun CY, Han YH, Hong US, Baek EG. Two cases of pneumonia treated with theory on epidemic febrile diseases. The Journal of Korean Oriental Internal Medicine. 2003;24 (3):705-711
22. Han DH, Jung HJ, Jung SK, Rhee HK. Clinical Study of Pneumonic Patients combined with Stroke. The Journal of Korean Oriental Internal Medicine. 2000;21(5):723-728.