

## 원저

## 퇴행성슬관절염에 대한 봉약침과 온침효과 비교

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## A Comparative study of Warm needling and Bee Venom Pharmacopuncture on Osteoarthritis of the Knee - a Randomized Controlled Trial -

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## ABSTRACT

- Objective** This study was performed to investigate whether Bee Venom Pharmacopuncture(BVP) could be a more effective modality than Warm Needling(WN) in relieving pain and symptoms of knee osteoarthritis(OA).
- Design** Prospective, randomized and controlled clinical trial.
- Setting** Single center trial in Korea
- Patients** 49 volunteers with knee OA participated in the study. All the participants were screened through an inclusion and exclusion criteria. 33 participants were completed the clinical trial.
- Intervention** The subjects were randomly assigned to one of two groups. One group received BVP(n=18), while the other group received WN(n=15). Sixteen sessions of BVP or WN were given at the pain region of the problematic knee for 8 weeks.
- Outcome measures** Primary outcome measure is the Korean translation of Western Ontario and McMaster Universities Osteoarthritis Index scores(Korean WOMAC, KWOMAC). Secondary outcome measure is the physical health scores based on the 36-Item Short-Form Health Survey(SF-36) and Patient Global Assessment(PGA). KWOMAC and SF-36 were measured third (baseline, 4 and 8 weeks). PGA was measured twice(4 and 8 weeks).
- Results** BVP group showed significant decrease compared to WN group in pain, function and total scores of KWOMAC according to the Mann-Whitney U-test. In the PGA, BVP group, compared to WN group, showed a significant increase.
- Conclusions** BVP was more effective in relieving pain of knee OA than WN. These findings suggest that BVP is a promising alternative for treating knee OA.

**key words** *Bee Venom Pharmacopuncture(BVP), warm needling(WN), osteoarthritis, KWOMAC, SF-36, Patient Global Assessment, Randomized Controlled Trial*

## I. Introduction

Knee osteoarthritis(OA) is a chronic progressive disease that is difficult to manage and control, discouraging both patients and medical doctors. Once knee OA develops on the knee, it results in a progressive deterioration of the pathological region of the knee, often accompanied by inflammation. A number of curative therapies for knee OA are not complete. So both pharmacologic and nonpharmacologic management focus on controlling pain and reducing functional limitation<sup>1)</sup>.

One of the important causes in knee OA is a external wind-cold-dampness(風寒濕)<sup>2)</sup>in oriental medicine. A external wind-cold-dampness result in the pain, edema, numbness, deformation, difficulty of bending and stretching of the knee joint. The knee OA therapeutics used in oriental medicine include acupuncture, bee venom pharmacupuncture(BVP), moxibustion, cupping, warm needling(WN) and herb medication. BVP has been used traditionally to relieve pain and treat OA due to its nociceptive effects on the thermal, visceral and inflammatory pain responses and considered to be a chemical moxibustion<sup>3,4)</sup>. Warm needling therapy(Fig. 1) is described in the Classic of Nourishing Life with Acupuncture and Moxibustion(鍼灸資生經)<sup>5)</sup> as combining the effects of acupuncture and moxibustion in a single treatment. In this technique, dried and pounded Folium Artemisiae Argyii(Ai Ye, or mugwort) is attached to the handle of the acupuncture needle after the needle has been inserted in an acupuncture point<sup>2)</sup>. Then the mugwort is lit and allowed to burn. Typically, there is about an inch between the surface of the skin and the ball of burning mugwort, and warmth is thus conducted from the handle of the needle to the needle itself and the surrounding tissue<sup>2)</sup>. This method is primarily appropriate for vacuity cold diseases and wind damp impediment conditions. Therefore Both BVP and WN were used mainly in a external wind-cold-

dampness tendency and chronic deficiency pattern disease; arthritis with soft tissue inflammation and musculoskeletal disease such as ligament sprain, traumatic inflammation, and lumbago in the previous reports<sup>6-10)</sup> and they have been especially thought to be a useful therapeutic approach to treat knee OA patients<sup>13-16)</sup>. On the basis of a few well controlled reports<sup>15,17)</sup> that corroborated the effectiveness of acupuncture alleviating pain and improving joint function, we investigated the clinical effectiveness of BVP in patients with knee OA by comparing the synergic therapeutic effect of BVP in the BVP group with that of moxibustion in WN group.

## II. Method

### 1. Target Population

Male and female volunteers were recruited through advertisements(Fig. 2). All patients signed an informed consent. This study was carried out under the supervision of an ethics committee(Hospital of Oriental Medicine, Kyung-won university).

#### 1) Inclusion criteria :

- Female or male from age of 50 to 70.
- Diagnosis of knee OA(American College of Rheumatology criteria applied).
- More than six-month knee OA Duration.
- Documented radiographic changes of osteoarthritis (Kellgren-Lawrence grade of 1 or more).
- Signed informed consent.

#### 2) Exclusion criteria :

- Female or male over the age of 70.
- Intra-articular corticosteroid injection in the knee within the four weeks immediately preceding the beginning of the trial.
- Severe chronic or uncontrolled concomitant illness.
- Diagnosis of rheumatoid arthritis of the knee.

- History or clinical indications of bleeding diathesis and cardiovascular disease, including current use of anticoagulants.
- Allergy to metal.
- Allergy to Bee Venom Pharmacupuncture
- History of anaphylaxis shock induced by bee venom
- In blood test, Rheumatoid Factor=1:40, Erythrocyte Sedimentation Rate=40mm/hour.
- Previous treatment with acupuncture within four weeks prior to entering the study.
- Taking hormone medications.
- Fearing about moxibustion and warm sensation.

## 2. Study design

### 1) Randomization

The subjects were divided into a BVP and a WN group through a random table generated by SPSS 12.0. Two operators licensed in oriental medicine, having over seven years' experience in clinical treatment, performed the acupuncture. The subjects of both groups were assigned to two operators.

### 2) Blinding and materials

Because it was impossible to blind the operators, both all subjects and the analyzers for the data were blinded.

## 3. Acupoint

We selected acupuncture point based upon the Oriental Traditional Medicine meridian theory to treat knee joint pain, known as the "Impediment(痺)" syndrome caused by a external wind-cold-dampness, which uses local points on channels that transverse the area of pain. The acupoints consisted of common and additional acupoint. Common acupoint is 4 local points used commonly on knee OA. Additional acupoint is the option of acupoint found on the diagnosis of the meridian ; 1~2 local points(Table 1).

The operators must use the common and the additional acupoint, however they are allowed to select one or two meridian. The total acupoint is about 4~6.

## 4. Procedure

This study was devised to find resolution to controversies over using sham intervention such as injection of normal saline to patients in the control group and violating the Ethics and to make each group comparable state in a light that BVP can be considered as a chemical moxibustion.

In the WN group, modified WN was actually applied to patients. That is, acupuncture was performed at the selected acupoints as shown in Table 1, where moxa sticks with wholes in the middle were then lit up and put with surrounding the handles of the needles (Fig. 1). The burning time was about 7~8 minutes. It was used only one time in a session. Twirling reinforcement-reduction methods were not used. Patients received modified warm needling treatments twice per week over an eight-week period. The depth of acupuncture was about 2~10mm, and the needles were retained about 20 minutes.

In the BVP group, BVP was also done at the selected acupoints as shown in Table 1. Bee venom acupuncture solution was made by dried bee venom from You-miel Bee Venom Ltd. through dilution (normal saline to dried bee venom=3000 to 1) and purification. The amount injected to a acupoint was restricted to 0.01mL and the whole amount injected to a patient will not exceed 0.2mL. Acupuncture was consecutively done at the same acupoints as soon as BVP was finished. Frequency and duration of BVP were same as those of WN group.

## 5. Measurement of the pain relief effects

To estimate the pain relief effects of BVP on knee OA and to compare with those of WN, the Korean translation of Western Ontario and

McMaster Universities Osteoarthritis Index(Korean WOMAC, KWOMAC) was used to measure the primary outcomes following eight weeks of treatment<sup>18)</sup>. As for the measurement of secondary outcomes, the 36-Items Short-Form Health Survey (SF-36) was used to estimate the quality of life at the pre-trial period, 4 and 8 weeks. In addition, the Patient Global Assessment was used to assess the improvement of the symptoms after eight weeks of treatment. The measurements were carried out with the evaluator groups thoroughly blinded. There were no side effects in any of the subject from either group.

## 6. Statistical analysis

The changes of the mean score between pre-trial baselines and post-trial outcomes in each group was assessed with Wilcoxon sign rank sum test and the difference of BVP and WN group in VAS, KWOMAC and SF-36 was assessed with a Mann-Whitney U-test at baseline, 4 and 8 week(SPSS 12.0).

### III. Results

The study was done to evaluate the effect of BVP on pain relief of degenerative knee OA and to compare it with that of warm needling for the same disease. The subjects who met both inclusion criteria and exclusion criteria from the recruited participants were selected(the participant flowchart is shown in Fig. 2). The demographic and baseline characteristics for both groups are shown in Table 2. In the table both groups exhibit similar characteristics in their general features and baseline outcomes. This means that the randomized assignment of the subjects was appropriate for this clinical study. During the trial, the number of dropouts was 7 in the BVP group and 9 in the WN

group, as shown in Fig. 2. The dropouts were classified as follows: in the WN group, 2 by discontinued study, and 7 by personal reasons; in the BVP group, 1 by other disease, and 6 by personal reason.

#### 1. According to VAS, KWOMAC and SF-36 scores, both BVP and WN were effective after 8 weeks' trial in the participants

The pre-trial VAS, KWOMAC and SF-36 total score were  $5.61 \pm 1.82$ ,  $27.11 \pm 13.81$  and  $51.56 \pm 13.53$  in the BVP group, which were changed to  $2.22 \pm 0.88$ ,  $12.89 \pm 9.68$  and  $63.36 \pm 11.03$  after 8 weeks' trial. Thus, VAS and KWOMAC total score in the BVP group showed significant decrease, while SF-36 total score showed significant increase, with Wilcoxon sign rank sum test( $p=0.000$ ). Consistent with the above, In WN, VAS and KWOMAC total score were also significantly decreased from  $6.07 \pm 1.33$  and  $26.73 \pm 11.07$  at baseline to  $2.93 \pm 0.07$  and  $17.67 \pm 8.30$  at 8 week( $p=0.001$ ), while SF-36 total score was significantly increased from  $52.71 \pm 9.42$  to  $61.37 \pm 8.8$ ( $p=0.001$ )(Table 3, 4, 5).

#### 2. According to VAS and function KWOMAC index scores, after 8 weeks' trial, BVP was found to be more effective than WN in the participants

The difference between VAS, total KWOMAC score and a function subscale score of KWOMAC at baseline and those after 8 weeks' trial in the BVP group was  $-3.39 \pm 1.50$ ,  $-14.44 \pm 8.41$  and  $-11.11 \pm 5.85$  respectively, which was found to be significant( $P<0.05$ ) compared to  $-3.13 \pm 0.99$ ,  $-9.07 \pm 6.36$  and  $-6.26 \pm 4.40$  in the WN group. meanwhile there was no significant difference between BVP and WN group in the other subscales of KWOMAC(Table 6).

**3. According to a SF-36 score, after 8 weeks' trial, Both BVP and WN were helpful to relieve pain and to improve other symptoms in the participants, but there was no actual significant difference between BVP and WN.**

The SF-36 total score was made up of physical and mental health score. The SF-36 total score, physical health score and mental health score had a tendency to be increased after 8 weeks' trial in the BVP group as well as in the WN group, which changed from pre-trial to post-trial was  $11.79 \pm 7.06$ ,  $15.12 \pm 9.24$  and  $8.37 \pm 8.62$  in BVP group, and  $9.66 \pm 5.27$ ,  $13.19 \pm 8.09$  and  $7.03 \pm 8.65$  in WN group.(Table 6).

**4. According to the Patient Global Assessment, after 8 weeks' trial, BVP was found to be more effective than WN in the participants.**

A Patient Global Assessment was carried out by the participants themselves at the end of the 8 weeks' trial in order to evaluate the condition of knee OA. Among the 18 participants in the BVP group, the distribution of the Patient Global Assessment was 16.6% in "Excellent", 55.5% in "Good", 27.9% in "Fair" and 0% in "Poor". The distribution among the 17 participants in the WN group was 6.6% in "Excellent", 53.3% in "Good", 40.1% in "Fair" and 0% in "Poor" ( $p=0.401$ )(Table 7).

#### IV. Discussion

Bee venom(BV) is known to be a very complex mixture of active peptides, including melittin(a major component of BV), phospholipase A2, apamin, adolapin, and mast cell-degranulating peptide(MCDP).

Many studies on the biological and pharmacological activities of BV have been carried out, through which

the anti-inflammatory and anti-rheumatoid arthritis effect, pain relief of BV have been described<sup>19-29</sup>.

BVP is a type of pharmacopuncture expected to get the synergic effect of acupuncture and BV. Besides the inflammatory effect of BV, BV has warm nature enough to eliminating Yin pathogen by promoting the circulation of meridian and is often considered to be a chemical moxibustion due to its similarity in action to moxibustion in the concept of korean traditional medicine.

Based upon the above, BVP is growing in clinical practice primarily used to relieve pain of inflammatory diseases including OA.

Warm needling is also a combined method of using acupuncture and moxibustion at the same time, in which the effects of acupuncture stimulation are known to be augmented by the moxibustion<sup>6</sup>. OA is usually induced by Yin pathogen such as cold and dampness. Therefore major principle of OA treatment is to eliminate the Yin pathogen and to facilitate the flow of blood circulation and thus relieve the pain, which is elaborated on that At the early and middle stages of knee OA, promoting blood circulation, eliminating hemostasis, and reducing edema and alleviating pain are recommended, and at later stage, promoting blood synthesis and warming meridians to reduce the pain via promoting circulation are recommended<sup>7</sup>. To maximize the treatment effect, BVP can be adopted for a useful treatment method as well as WN.

To determine whether BVP is more effective than WN, We evaluated the therapeutic effectiveness of BVP compared to that of WN. The results of our study indicated that patients with knee OA showed significant improvement after 8 weeks of either BVP or WN according to VAS, KWOMAC and SF-36 scores. The BVP group showed significant difference in relieving pain and improving symptoms of participants with knee OA compared to the WN group according to VAS, function and total score of KWOMAC after 8 weeks' trial, but, on pain and stiffness subscales of KWOMAC, SF-

36 and Patient Global Assessment, there was little difference between BVP and WN.

There are some reports and ongoing studies to investigate the effectiveness of acupuncture treating knee OA. Some studies have established the effectiveness of acupuncture treatment in relieving both the pain and dysfunction of the knee in elderly patients with knee OA in comparison to non-acupuncture treated control groups<sup>13,17</sup>. Some reports<sup>13-14,30-33</sup> also showed significant pain relief in patients treated with acupuncture compared to sham acupuncture, exercise and education, and Wait-List control group. On the contrary, other reports<sup>34-35</sup> showed no significant difference in pain reduction between acupuncture and sham acupuncture or Wait-List control group. Therefore we need not only to participate in ongoing studies reconfirming the effect of acupuncture treatment for knee OA but to seek the changes on most researchers' monotonous designs of the study. In this study, we investigated the effectiveness of BVP for knee OA because of its more frequent use and better known clinical effectiveness in patients with knee OA. Moreover we chose the WN group as positive control group for three good reasons. One was our concern that it is not actually easy to compare Pharmacopuncture with acupuncture directly. Another was because BV has same warm characteristic as Moxibustion and it can be regarded as chemical moxibustion. The third came from the idea that BVP can be also made similar to WN, if only acupunctured again at the same acupoint where BVP was done.

We expect this study would be helpful to elucidate the effect of the acupuncture from other published reports<sup>13,30-31,33-34</sup>, and we are looking forward to investigating the effect of other interventions available for clinical practice and ultimately to finding a alternative way to manage OA more efficiently in the near future.

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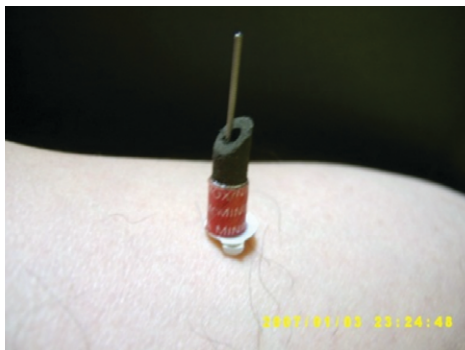


Fig. 1. The feature of warm needling.

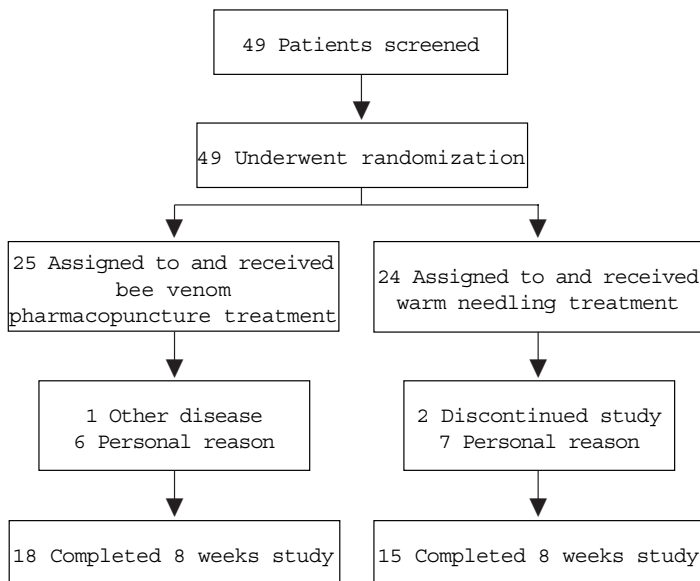


Fig. 2. Participant flowchart.



Table 1. Acupoints.

Standard Acupoint		Ex-LX4 (Xiyan), ST <sub>35</sub> , ST <sub>36</sub> , Ex-LE <sub>2</sub> (Heding)	
Meridian Acupoint	Pain at upper and dorsal to the medial condyle of the tibia	Spleen	SP <sub>9</sub> , SP <sub>10</sub>
	Pain at the medial end of the popliteal crease, dorsal to the medial condyle of the tibia	Liver	LR <sub>8</sub>
	Pain at ventral and distal to the head of the fibula	Gall	GB <sub>34</sub> , GB <sub>33</sub>
	Pain in the middle of the popliteal fibula crease	Urinary	BL <sub>40</sub>
	Pain at the lower edge of the patella, lateral to the patella ligament	Stomach	ST <sub>34</sub>
	Pain in the medial part of the popliteal fossa between the tendons of the semi-tendinosus and semi-membranosus muscles	Kidney	KI <sub>10</sub>
A-Shi	region of tenderness		1-4

Table 2. The participant demographic and baseline characteristics\*.

Characteristic	Bee venom pharmacopuncture (n)	Warm needling (n=15)	Total (n=33)
age(yr)	58.83	59.87	59.30
Gender			
Female	17 (94.4%)	14 (93.3%)	31 (93.9%)
Male	1 (5.6%)	1 (6.7%)	2 (6.1%)
Total	18 (100%)	15 (100%)	33 (100%)
Weight (Kg)	61.00	56.60	59.00
Height (cm)	156.94	156.33	156.67
BMI	24.77	23.16	24.04
K-L grade			
1	11 (61.1%)	7 (46.7%)	18 (54.5%)
2	5 (27.8%)	6 (40.0%)	11 (33.3%)
3	2 (11.1%)	2 (13.3%)	4 (12.1%)
Total	18 (100%)	15 (100%)	33 (100%)
Meridian			
Spleen(脾經)	9 (50.0%)	9 (60%)	18 (54.5%)
Stomach(胃經)	5 (27.8%)	4 (26.6%)	9 (27.3%)
Gall bladder(膽經)	2 (11.1%)	1 (6.7%)	3 (9.1%)
Urinary bladder(膀胱)	2 (11.1%)	1 (6.7%)	3 (9.1%)
Target knee			
Right	9 (50.0%)	9 (60%)	18 (54.5%)
Left	9 (50.0%)	6 (40%)	15 (45.5%)
Outcomes			
KWOMAC pain score	4.50	4.40	
KWOMAC stiffness score	1.83	1.67	
KWOMAC function score	20.78	20.67	
KWOMAC total score	27.11	26.73	
SF-36 physical score	48.91	47.36	
SF-36 mental score	53.42	58.67	
SF-36 mental score	51.56	52.71	

\* There were no statistically differences between the Warm needling group and the Acupuncture group at baseline. Values expressed with a sign are means. KWOMAC=Korean Western and McMaster Universities Osteoarthritis Index. SF 36=36-Item Short-Form Health Survey. VAS=Visual Analogue Scale

Table 3. The changes of the VAS score in Bee venom pharmacopuncture and warm needling group.

	VAS score		P-value
	baseline	8 weeks	
Bee venom pharmacopuncture	5.61±1.82	2.22±0.88	0.000*
Warm needling	6.07±1.33	2.93±0.70	0.001*

The result and P-value from the Wilcoxon sing rank sum test with the changes from baselines. The values presented with a plus/minus sign are means's.

Table 4. The changes of the KWOMAC total score in Bee venom pharmacopuncture and

	KWOMAC total score		P-value
	baseline	8 weeks	
Bee venom pharmacopuncture	27.11±13.81	12.89±9.68	0.000*
Warm needling	26.73±11.07	17.67±8.30	0.001*

The result and P-value from the Wilcoxon sing rank sum test with the changes from baselines. The values presented with a plus/minus sign are means's.

Table 5. The changes of the SF-36 total score in Bee venom pharmacopuncture and

	SF-36 total score		P-value
	baseline	8 weeks	
Bee venom pharmacopuncture	51.56±13.53	63.36±11.03	0.000*
Warm needling	52.71±9.42	61.37±8.80	0.001*

The result and P-value from the Wilcoxon sing rank sum test with the changes from baselines. The values presented with a plus/minus sign are means's.

Table 6. The changes of the mean score between pre-trial baselines and post-

	Bee venom pharmacopuncture	Warm needling	P-value
<sup>a</sup> VAS	-3.39±1.50	-3.13±0.99	0.033*
<sup>b</sup> KWOMAC			
KWOMAC total	-14.44±8.41	-9.07±6.36	0.044*
KWOMAC pain	-2.11±1.28	-1.67±1.40	0.421
KWOMAC stiffness	-1.00±1.41	-1.13±1.30	0.509
KWOMAC function	-11.11±5.85	-6.27±4.40	0.027*
<sup>c</sup> SF-36			
SF-36 total	11.79±7.06	9.66±5.27	0.656
SF-36 physical health	15.12±9.24	13.19±8.09	0.442
SF-36 mental health	8.37±8.62	7.30±8.65	0.630

The result and P-value from the Mann-Whitney U-test with the changes from baselines. The values presented with a plus/minus sign are means's.

<sup>a</sup>VAS=Visual Analogue Scale.

<sup>b</sup>KWOMAC=Western Ontario and McMaster Universities Osteoarthritis Index translated into Korean language.

<sup>c</sup>SF-36=36-Items Short-Form Health Survey.

Table 7. Patient Global Assessment at the end of 8 weeks in participant

	Poor	Fair	Good	Excellent	P-value
Bee venom pharmacopuncture	0	5	10	3	0.401
Warm needling	0	6	8	1	

The result and P-value from Mann-Whitney U-test after 8 weeks.

Numbers indicate the number of the subjects who rated each level of improvement of the disease