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Original Article

Analgesic and warming meridians as well as unblocking collateral effects of needle warming moxibustion in patients with osteoarthritis of the knee joint

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Abstract: Objective: To examine the clinical effect and significance of needle warming moxibustion in the treatment of knee osteoarthritis (KOA). Methods: As research subjects, 412 patients with KOA who received treatment at the rheumatism immunity department of our hospital were selected. The patients were divided into groups according to clinical treatment. Needle warming moxibustion therapy was used in the study group, and sodium hyaluronate injection, in the control group, with 206 cases included in each group. Clinical efficacy of each treatment was observed. Results: Before the treatment, pain, stiffness, daily activity, and comprehensive scores were not significantly different between the two groups ($P > 0.05$). A variance analysis of the repeated measurement revealed that 3, 6, and 9 weeks after the treatment, the pain, stiffness score, daily activity, and comprehensive scores were significantly lower in the study group than in the control group (all $P < 0.01$) and significantly lower than those before treatment ($P < 0.01$). The total effective rate in the study group was significantly higher than that in the control group ($P < 0.01$). Conclusion: Needle warming moxibustion for the treatment of knee osteoarthritis can effectively relieve the symptoms of pain and stiffness in patients with KOA and has the effects of warming meridians and unblocking collaterals. In the treatment course, no discomfort or adverse reaction was observed, and the patients with KOA were better rehabilitated with improvement in their quality of life. Therefore, needle warming moxibustion is worthy of clinical application.

Keywords: Needle warming moxibustion, knee osteoarthritis, analgesic effect, sodium hyaluronate

Introduction

Arthritis is a common human disease and is classified into many clinical categories such as rheumatoid arthritis, tuberculous arthritis, and osteoarthritis, which is also called hypertrophic and degenerative arthritis [1]. The knee joint is the most important weight-bearing joint in the human body with the most activities and the largest load. Therefore, the incidence of knee osteoarthritis (KOA) has always been increasing [2]. KOA is a human pathological disease that presents degeneration of the articular cartilage and synovial tissues and hyperplasia of the articular bone caused by the synthesis maladjustment of the subchondral bone and cartilage cells, extracellular matrix, etc., under the combined action of biological and mechanical factors [3]. Research shows that KOA is prevalent in the elderly, with an incidence of approximately 60% in the population of > 60 years old and 80% in the population of > 70 years old, showing increasing trends with aging and increasing obesity rate [4].

As KOA progresses, the human knee joint is gradually destroyed, and the pathological changes induce joint structure disorders that clinically manifest as knee pain, swelling, morning stiffness, and less joint stability, or even joint deformity and functional disorders in cases of serious illness, which seriously affects the quality of life of patients and exerts psychological damage to the patient [5]. KOA belongs to the "arthromyodynia" category in the traditional Chinese medicine and is known as "knee

Table 1. Comparison of basal line date between the study and control groups [example (%)] ($\bar{x}$ ± SD)

Classification	The team (n = 206)	The control group (n = 206)	$t/\sum^2$	P
Gender			0.492	0.548
Male	125 (60.68)	118 (57.28)		
Female	81 (39.32)	88 (42.72)		
Age	66.1±5.4	66.7±4.3	1.248	0.212
Disease course	3.6±0.8	3.7±1.0	1.121	0.263
Disease type			1.058	0.589
Elderly	127 (61.65)	137 (66.50)		
Trauma	50 (24.27)	44 (21.36)		
Inflammation	29 (14.08)	25 (12.14)		

paralysis", "arthritis", and "muscle rheumatism", etc. [6]. The present study shows that the disease is internally caused by deficiencies of the liver, spleen, and kidney, and externally results from invasion by wind, cold, and wet, which leads to muscle dystrophy and stagnation of qi and blood. When the diseases persist, phlegm and blood stasis and the meridian barrier occur with pain, which is an illness caused by the combination reaction of the body deficiency and adverse environment [7]. At present, the main purpose of the KOA treatment is to relieve pain, relieve inflammatory swelling, and improve the activity relaxation ability of the knee joint [8]. Currently, many patients give up or discontinue the treatment because of its lower efficacy with obvious adverse reactions and toxic side effects. Therefore, how to effectively treat the disease and improve the quality of life of these patients has always been an important issue in clinical research.

With development of medical levels, traditional Chinese medicine presents some advantages in treating KOA with the clinical characteristics of low cost, convenience, obvious therapeutic effect, and little toxic side effects [9]. Among which, the needle warming moxibustion method is characteristic of the traditional Chinese medicine. Needle warming moxibustion achieves the effect of treatment and prevention of disease by selecting the corresponding points in the human body and applying the moxibustion fire to give the patient warm stimulation and so on [10]. At present, little research has been conducted on the application of needle warming moxibustion in patients with KOA. In this study, patients with KOA were treated with needle warming moxibustion to observe the specific therapeutic effect and provide reference for clinical practice.

Material and methods

General information

As research subjects, 412 patients with KOA, who received treatment at the Rheumatism Immunity Department of our hospital were included. The patients were divided into groups according to clinical treatment. Needle warming moxibustion therapy was used in the study group; and sodium hyaluronate injection, in the control group, with 206 cases in each group. The study group was composed of 125 men and 81 women aged 47-86 years (mean, 64.7 ± 5.4 years). The disease duration ranged from 5 months to 11 years (mean, 3.6 ± 0.8 years). In the group, 186 patients were elderly, 58 patients had trauma, 39 cases were caused by inflammatory diseases, and 65 had hypertension. In the Western medicine group, 88 patients were men and 118 were women, aged 45-87 years (mean, 66.7 ± 4.3 years). The disease duration ranged from 6 months to 12 years (mean, 3.7 ± 1.0 years). In the group, 147 patients were elderly, 68 patients had trauma, 50 cases were caused by inflammatory diseases, and 51 patients had combined hypertension. No significant differences in sex, age, or type of disease were found between the study and control groups and the two groups were comparable (P > 0.05, **Table 1**).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) patients who met the diagnostic criteria for KOA according to the American Society of Rheumatology; (2) patients with positive patellar grinding test results; (3) patients who agreed to participate in the clinical research and provided informed consent. The exclusion criteria were as follows: (1) patients who had undergone knee therapy before treatment; (2) patients with symptoms of fever or skin infection in the lesion parts; (3) patients with severe liver, kidney, and hematopoietic dysfunction; (4)

patients with a combination of other osseous diseases such as gout and bone cancer; (5) patients with mental disease or a family history of mental illness; and (6) patients aged ≤ 39 and ≥ 88 years.

Treatment methods

The study group: In this group, needle warming moxibustion therapy was used for the treatment. The patients were placed in a supine posture, with the knee joint naturally bent at 45°. The internal and external knee eyes, and the Liangqiu, Xuehai, and Zusanli points were selected for acupuncture. After conventional local disinfection, a 0.35- × 50-mm acupuncture needle (Guangzhou Deyuan Medical Devices, Co., Ltd., with Jiangsu FDA Medical Devices License No. 20010020) was quickly inserted, lifted, and twisted. After the acupuncture feeling was attained, a 2-cm moxa stick (Suzhou Dongfang Moxa Factory, No. Z32021062) was installed to the needle handle at each point, which was 4 cm away from the skin. The moxa stick was lighted, and needle warming moxibustion was conducted with two columns of the lighted stick. The needles were kept for 35 min, and the acupuncture was conducted 6 times each week and continued for 9 weeks total time.

The patients in the control group were treated with intra-articular injection of sodium hyaluronate. The patients were placed in the supine posture, with the knee joint naturally bent at 45°. The position of the inner knee eye was selected as the needle point. Routine local disinfection was conducted, and continuous needle injection of 1.5 ml of sodium hyaluronate (Shanghai Haohai Biological Polytron Technologies Inc, H20051837) was performed. The needle was pulled out rapidly after the injection, and wound plaster was applied on the wound topically. The injection was given 6 times per week for 9 weeks.

Observation of curative effect

The condition was evaluated by adopting the Osteoarthritis Index (WOMAC) of Xi'an Ontario and McMaster University [11]. WOMAC is the best checklist for KOA in three aspects, including knee and hip osteoarthritis pain, joint stiffness, and daily activities. The total pain, stiffness, and daily activity scores were 20, 8, and 68, respectively, with a total of 96 points. The higher score indicated more serious condition.

Result determination

Symptom improvement and function recovery were evaluated using the WOMAC score before treatment and at 3, 6, and 9 weeks after the treatment. In the nimodipine method [12], recovery was described as an efficacy index of ≥ 80%; excellence, as 50% ≤ efficacy index < 80%; effectiveness, as 25% ≤ efficacy index < 50%; and ineffectiveness, as an efficacy index of < 25%.

Safety evaluation

The adverse reactions and toxic side effects experienced by the patients during treatment with needle warming moxibustion were recorded.

Statistical method

SPSS17.0 (Tianjin Soft Kewang Science and Technology Co., Ltd.) was used for the statistical analysis. Mean ± the standard deviation ($x \pm SD$) was used to express the measurement data, and the two-sample t test was adopted. The counting data are expressed as a percentage, and the Chi square test was used for the analysis. The data at multiple time points were compared using variance analysis of repeated measurement followed with post-hoc t-test. A P value of < 0.05 indicated statistical difference.

Results

Baseline data of patients in the study group and control group

There was no statistically significant difference in the sex, age, and disease type between the study group and the control group, and they were comparable (P > 0.05) (**Table 1**).

Pain score before and after treatment in the study and control groups

Before the treatment, the pain score of the patients in the study group showed no significant difference with that of the patients in the control group (P > 0.05). After 3 weeks treatment, the pain score of the study group was significantly lower than that of the control group (t = 6.185, P<0.001). After 6 weeks of treat-

Table 2. Pain scores before and after treatment in the study and control groups ($\bar{x}$ ± SD)

Treatment time	The team (n = 206)	The control group (n = 206)	t	P
Before the treatment	14.8 ± 3.6	14.3 ± 3.3	1.469	0.142
Treatment for 3 weeks	10.3 ± 2.8[a]	12.1 ± 3.1[a]	6.185	< 0.001
Treatment of 6 weeks	8.6 ± 2.7[a,b]	10.7 ± 3.2[a,b]	7.199	< 0.001
Treatment of 9 weeks	7.9 ± 2.4[a,b,c]	9.16 ± 3.1[a,b,c]	4.613	< 0.001
F	234.200	97.330		
P	< 0.001	< 0.001		

[a]P < 0.01, compared with that before treatment. [b]P < 0.01, compared with that at 3 weeks after treatment. [c]P < 0.01, compared with that at 6 weeks after treatment.

Table 3. Stiffness scores before and after treatment in the study and control groups (x ± SD)

Treatment time	The team (n = 206)	The control group (n = 206)	t	P
Before the treatment	6.2 ± 2.7	6.5 ± 2.3	1.214	0.225
Treatment for 3 weeks	4.9 ± 2.2[a]	5.5 ± 2.1[a]	2.831	0.004
Treatment of 6 weeks	4.1 ± 2.0[a,b]	4.9 ± 2.9[a,b]	3.259	0.001
Treatment of 9 weeks	3.6 ± 1.8[a,b,c]	4.1 ± 2.3[a,b,c]	2.457	0.014
F	54.730	36.040		
P	< 0.001	< 0.001		

[a]P < 0.01, compared with that before treatment. [b]P < 0.01, compared with that at 3 weeks after treatment. [c]P < 0.01, compared with that at 6 weeks after treatment.

ment, the pain score of the study group was significantly lower than that of the control group (t = 7.199, P < 0.001) and lower than 3 weeks treatment (t = 6.273, P < 0.001). After 9 weeks treatment, the pain score of the study group was significantly lower than that of the control group (t = 4.613, P < 0.001), and lower than 6 weeks treatment (t = 2.781, P = 0.005). (P < 0.01; **Table 2**).

Stiffness scores of the patients in the study and control groups before and after treatment

Before treatment, the stiffness score of the patients showed no significant difference between the study and control groups (P > 0.05). After 3 weeks treatment, the stiffness score of the study group was significantly lower than that of the control group (t = 2.831, P = 0.004); after 6 weeks of treatment, the stiffness score of the study group was significantly lower than that of the control group (t = 3.259, P = 0.001) and lower than 3 weeks treatment (t = 3.862, P < 0.001). After 9 weeks treatment, the stiffness score of the study group was significantly lower than that of the control group (t = 2.457, P = 0.014), and lower than 6 weeks treatment (t = 2.667, P = 0.008) (**Table 3**).

Daily activity scores in the study and control groups before and after treatment

Before treatment, the daily activity score of the patients showed no significant difference between the study and control groups (P > 0.05). After 3 weeks of treatment, the daily activity score of the study group was significantly lower than that of the control group (t = 8.041, P < 0.001). After 6 weeks of treatment, the daily activity score of the study group was significantly lower than that of the control group (t = 6.519, P < 0.001) and lower than 3 weeks treatment (t = 7.987, P < 0.001). After 9 weeks of treatment, the daily activity scores of the study group were significantly lower than the control group (t = 7.003, P < 0.001) and lower than 6 weeks treatment (t = 6.564, P < 0.001) (**Table 4**).

Comprehensive scores of the patients in the study and control groups before and after treatment

Before treatment, the comprehensive score of the patients showed no significant difference between the study and control groups (P > 0.05). After 3 weeks of treatment, the overall

Table 4. Daily activity scores in the study and control groups before and after treatment (x ± SD)

Treatment time	The team (n = 206)	The control group (n = 206)	t	P
Before the treatment	57.2 ± 12.7	55.1 ± 11.8	1.739	0.082
Treatment for 3 weeks	38.6 ± 9.1[a]	46.3 ± 10.3[a]	8.041	< 0.001
Treatment of 6 weeks	31.7 ± 9.6[a,b]	38.4 ± 11.2[a,b]	6.519	< 0.001
Treatment of 9 weeks	26.1 ± 7.6[a,b,c]	31.7 ± 8.6[a,b,c]	7.003	< 0.001
F	383.2	189.0		
P	< 0.001	< 0.001		

[a]P < 0.01, compared with that before treatment. [b]P < 0.01, compared with that at 3 weeks after treatment. [c]P < 0.01, compared with that at 6 weeks after treatment.

Table 5. Comparison of comprehensive scores between the study and control groups before and after treatment (x ± SD)

Treatment time	The team (n = 206)	The control group (n = 206)	t	P
Before the treatment	87.1 ± 13.7	85.7 ± 11.9	1.107	0.268
Treatment for 3 weeks	68.4 ± 10.6[a]	76.1 ± 11.5[a]	7.066	< 0.001
Treatment of 6 weeks	46.3 ± 8.4[a,b]	61.7 ± 9.6[a,b]	17.330	< 0.001
Treatment of 9 weeks	39.8 ± 7.1[a,b,c]	52.3 ± 7.6[a,b,c]	17.250	< 0.001
F	913.4	428.7		
P	< 0.001	< 0.001		

[a]P < 0.01, compared with that before treatment. [b]P < 0.01, compared with that at 3 weeks after treatment. [c]P < 0.01, compared with that at 6 weeks after treatment.

score of the study group was significantly lower than that of the control group (t = 7.066, P < 0.001). After 6 weeks of treatment, the comprehensive score of the study group was significantly lower than that of the control group (t = 17.330, P < 0.001) and lower than 3 weeks treatment (t = 19.210, P < 0.001). After 9 weeks of treatment, the comprehensive score of the study group was significantly lower than that of the control group (t = 17.250, P < 0.001) and lower than 6 weeks treatment (t = 8.482, P < 0.001) (**Table 5**).

Comprehensive effect in the study and control groups

The comprehensive efficacy comparison between the study and control groups revealed that the total efficacy rates in the study and control groups significantly differed (97.57% vs 84.46%; P < 0.01), which suggests that the long-term curative effect of needle warming moxibustion was better (**Table 6**).

Safety analysis of the needle warming moxibustion treatment

No discomfort and toxic side effects were observed in the patients during the experiment.

Discussion

KOA is a degenerative disease of the articular cartilage and synovial tissue, and a common pathological disease with the dominant presence of bone hyperplasia at the edge of the joint. Most patients are elderly women, and the incidence of the disease tends to increase with aging [13]. Studies have shown that KOA often causes inflammatory reaction in the surrounding cartilage tissue due to articular cartilage lesions, and the pathological process is complex and irreversible, which not only brings inconvenience to daily life but also causes a heavy burden to the patient's family [14]. Therefore, to eliminate stiffness and pain of the knee joint and improve the daily life of patients have always been the main purpose of clinical treatment.

In traditional Chinese medicine, KOA belongs to the category "arthralgia syndrome", whose causes were earliest recorded in "Huangdi Neijing" [15]. "Zhang Tong Medicine - Knee Pain" [16] recorded that "the knee is the mansion of tendon and all knee pains are due to liver and kidney deficiency in addition to the invasion of cold and moisture". "Su Wen" [17] indicated that the combined effect of cold,

Table 6. Comparison of comprehensive efficacy between the study and control groups (n [%])

Group	N	Heal	Excellence	Effective	Invalid	Total effective rate
The team	206	51 (24.76)	107 (51.94)	43 (20.87)	5 (2.43)	97.57
The control group	206	21 (10.19)	88 (42.72)	65 (31.55)	32 (15.53)	84.46
x^2	-		38.535			21.647
P	-		< 0.001			< 0.001

wind, and moisture induces arthralgia syndrome. Therefore, most people think that the main cause of the disease is liver and kidney deficiencies in muscle dystrophy and that the cold invades the knee because of the deficiencies and stays in the joint muscles, which results in qi stagnation and blood stasis, which correlates with liver and kidney functions [18]. Research studies demonstrated that most KOA patients have histories of knee cold pain or overwork, and the disease will worsen at different degrees in rainy weather conditions [19].

Acupuncture and moxibustion treatment of KOA has its own clinical characteristics and advantages. Owing to its remarkable curative effect and nontoxic side effects, it has been widely recognized, with accumulated rich experience in clinical practice [20]. Research shows that the main pathological mechanism of the knee joint is the intraosseous microcirculation changes caused by local congestion of the joint. In acupuncture, stabs in acupoints can evacuate the cold and unblock collaterals, and improve blood circulation and blood supply, thereby relieving the pain and stiffness of the knee joint [20]. Needle warming moxibustion has a better effect on the hyperosteogeny of the knee joint. It can make the tip of the bone hyperplasia blunt and further reduce the wear of the knee joint surface to relieve pain and improve the stiffness and swelling of the joints [10]. In needle warming moxibustion, a drug with heating energy is used for moxibustion, with the effects of unblocking collaterals and dispelling damp and cold. In combination with acupuncture, the heat can be transmitted to the Yuacu points through the needle body to dispel the moisture and cold, ventilate the blood stasis, relieve the knee muscle spasm, remove adhesions of the joint soft tissue, stimulate qi, with better efficacy for patients with deeper deficiency of venereal disease [21].

Considering the etiology of KOA, we chose the internal and external knee eyes, and Liangqiu, Xuehai, and Zusanli as acupoints. The internal and external knee eyes are common tenderness points of knee pain and have strong sensitivity to pain. After acupuncture at this point, the body can release an analgesic substance to relieve the knee joint pain [15]. Liang Qiu belongs to the stomach meridian of Yangming, and acupuncture at the point enables blood supplementation after birth, making the Qi and blood unobstructed, dredge the meridians, and achieve an analgesic effect [16]. Xuehai belongs to the stomach meridian of the foot Yangming, with the effect of introducing blood to the spleen. With its location on the knee joint, it is the primary site for knee pain and stiffness, and acupuncture at the point will directly reach the root of the disease [22]. The Zusanli point is the major point for health care and belongs to the Yangming meridian acupoints, and the acupuncture on the site can supplement the blood and energy, adjust the spleen and stomach, and activate collaterals, as well as alleviate the severity of the illness [13]. The results of this study showed that at 3, 6, and 9 weeks after the treatment, the pain, stiffness, daily activity, and comprehensive scores in the study group were significantly lower than those in the control group and decreased greatly after treatment, which suggests that needle warming moxibustion improved the pain, stiffness, and quality of life of the patients with KOA, at a total efficacy rate of 97.57% without toxic side effects. The analysis revealed that the physical and chemical factors are produced under the combustion moxibustion and stimulate the Yu point through the body of the needle, along the peripheral nerve, conducting the central nervous system. In the process of transfer, it modulates and combines with all levels of central nerves, and thereby regulating the nerve, endocrine, and circulation system in the body. By warm stimulation of the body through thermal moxibustion fire, the effects that lead to meridian and pain relief are achieved. This is similar to the finding of the

study by Zhang et al. [23] that the acupuncture can warm meridians, dispel dampness and cold, and achieve swelling and pain relief. It can relieve pain and stiffness of knee joints, and promote the recovery of the motion function of the knee joint.

The inheritance of traditional Chinese medicine for thousands of years has achieved good curative effect in clinic settings, and the existing literature confirmed that acupuncture treatment of KOA has achieved good performance, but the specific mechanism of needle warming moxibustion as KOA treatment is unified, which results in the insufficient credibility of the treatment method. The relationship between acupuncture quantity and methods, and the amount of stimulation by needle warming acupuncture were not investigated in this study. In addition, long-term follow-up of the patients with KOA after treatment was not conducted, which is a limitation of this study. Therefore, in the next study, combined with the existing scientific and technological methods, the specific mechanism of acupuncture and moxibustion for the treatment of KOA will be further validated by strictly selecting acupoints and controlling the needle stimulation quantity to improve the credibility of the diagnosis and treatment, and provide reference for clinical application of acupuncture and moxibustion in the treatment of KOA.

In conclusion, acupuncture and moxibustion for the treatment of KOA will effectively relieve pain and stiffness, and achieve the effects of relieving pain and warming meridians, as well as unblocking collaterals. In the course of treatment, no discomfort or adverse or toxic reaction was observed in the KOA patients, and the patients showed better rehabilitation and quality of life, which promotes applicability of the treatment method.

Disclosure of conflict of interest

None.

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References

[1] McInnes IB and Schett G. Pathogenetic insights from the treatment of rheumatoid arthritis. Lancet 2017; 389: 2328-2337.

[2] McAlindon TE, LaValley MP, Harvey WF, Price LL, Driban JB, Zhang M and Ward RJ. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. JAMA 2017; 317: 1967-1975.

[3] Alfredo PP, Bjordal JM, Junior WS, Martins RÁBL, Stausholm MB, Casarotto RA, Marques AP and Joensen J. Long-term results of a randomized, controlled, double-blind study of low-level laser therapy before exercises in knee osteoarthritis: laser and exercises in knee osteoarthritis. Clin Rehabil 2018; 32: 173-178.

[4] Stausholm M, Bjordal J, Lopes-Martins R and Joensen J. Methodological flaws in meta-analysis of low-level laser therapy in knee osteoarthritis: a letter to the editor. Osteoarthritis Cartilage 2017; 25: e9-e10.

[5] Zheng J, Zhang H and Liu J. Different acupuncture and moxibustion methods at heding (EX-LE 2) for knee osteoarthritis with yang-deficiency and cold-stagnation syndrome. Zhongguo Zhen Jiu 2017; 37: 594-598.

[6] Zhu LL, Zhou JY, Luo L, Wang X, Peng JX, Chen SS, Yin HY, Wu QF, Zhang CS, Lv P, Tang Y and Yu SG. Comparison of the efficacy between conventional moxibustion and smoke-free moxibustion on knee osteoarthritis: study protocol of a randomized controlled trial. Trials 2017; 18: 188.

[7] Chen M, Hu R, Lin J, Huang Y, Mao W, Wen Y and Dai G. Aconite cake-separated moxibustion for knee osteoarthritis with kidney-marrow deficiency. Zhongguo Zhen Jiu 2018; 38: 45-49.

[8] Wang B, Hu J, Zhang N, Wang J, Chen Z and Wu Z. Clinical study of fire acupuncture with centro-square needles for knee osteoarthritis. Zhongguo Zhen Jiu 2017; 37: 463-466.

[9] Wang X, Hou M, Wang H and Ji F. Warm-needling moxibustion for knee osteoarthritis: a randomized controlled trial. Zhongguo Zhen Jiu 2017; 37: 457-462.

[10] Zhang YL, Gang JH, Wang HM and Mi YQ. Warming acupuncture affects TTX-R sodium current of DRG and PGE2 of KOA rats. Biomed Res 2017; 28.

[11] Katz N, Conaghan P, Kivitz A, Turk D, Johnson J, Kelley S and Bodick N. Assay sensitivity of average daily pain (ADP) and western ontario and mcmaster osteoarthritis index A-pain (WOMAC-A) in a phase 3 trial of intra-articular

FX006 for osteoarthritis knee pain. The Journal of Pain 2018; 19: S76.
[12] Pietrosimone B, Luc BA, Duncan A, Saliba SA, Hart JM and Ingersoll CD. Association between the single assessment numeric evaluation and the western ontario and mcmaster universities osteoarthritis index. J Athl Train 2017; 52: 526-533.
[13] Ren G, Lutz I, Railton P, Wiley JP, McAllister J, Powell J and Krawetz RJ. Serum and synovial fluid cytokine profiling in hip osteoarthritis: distinct from knee osteoarthritis and correlated with pain. BMC Musculoskelet Disord 2018; 19: 39.
[14] Kraus V, Conaghan P, Aazami H, Mehra P, Kivitz A, Lufkin J, Hauben J, Johnson J and Bodick N. Synovial and systemic pharmacokinetics (PK) of triamcinolone acetonide (TA) following intra-articular (IA) injection of an extended-release microsphere-based formulation (FX006) or standard crystalline suspension in patients with knee osteoarthritis (OA). Osteoarthritis Cartilage 2018; 26: 34-42.
[15] Li M, Yuan H, Wang P, Xin S, Hao J, Liu M, Li J, Yu M and Zhang X. Influences of De Qi induced by acupuncture on immediate and accumulated analgesic effects in patients with knee osteoarthritis: study protocol for a randomized controlled trial. Trials 2017; 18: 251.
[16] Yang G, Su Y and Guo Y. Acupuncture like transcutaneous electrical nerve stimulation (Tens) on knee osteoarthritis (KOA) with low pain: a pilot study. Int J Clin Exp Med 2017; 10: 1059-1065.
[17] Kong F, Chen J, Hu L, Zhang W and Zhou W. Observation of different acupuncture methods for injury of supra interspinous ligament. Journal of New Chinese Medicine 2017; 1: 047.
[18] Ma SN, Xie ZG, Guo Y, Yu JN, Lu J, Zhang W, Wang LJ, Xu J, Zhao RL, Zhou S and Guo CQ. Effect of acupotomy on FAK-PI3K signaling pathways in KOA rabbit articular cartilages. Evid Based Complement Alternat Med 2017; 2017: 4535326.
[19] Wang C, Wang X and Wu H. Overview on clinical and mechanism studies of acupuncture and moxibustion treatment of knee osteoarthritis. Traditional Chinese Medicine 2017; 6: 169-174.
[20] Sun N, Shi GX, Tu JF, Li YT, Zhang LW, Cao Y, Du Y, Zhao JJ, Xiong DC, Hou HK and Liu CZ. Traditional Chinese acupuncture versus minimal acupuncture for mild-to-moderate knee osteoarthritis: a protocol for a randomised, controlled pilot trial. BMJ Open 2016; 6: e013830.
[21] Li A, Wei ZJ, Liu Y, Li B, Guo X and Feng SQ. Moxibustion treatment for knee osteoarthritis: a systematic review and meta-analysis. Medicine 2016; 95: e3244
[22] Wang B, Liu X, Hu Z, Sun A, Ma Y, Chen Yingying, Zhang X, Liu M, Wang Y, Wang S, Zhang Y, Li Y and Shen W. YANG's pricking-cupping therapy for knee osteoarthritis: a multi-center randomized controlled trial. Zhongguo Zhen Jiu 2016; 36: 113-118.
[23] Zhang Y, Mi Y, Gang J and Wang H. Effects of warm needling moxibustion on knee cartilage and morphology in rats with knee osteoarthritis. Zhongguo Zhen Jiu 2016; 36: 175-179.