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Original Article

Local phonophoresis of traditional Chinese herbs: a good assistant for analgesia after total knee arthroplasty

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Abstract: Objectives: To evaluate the effect of local phonophoresis of Traditional Chinese Herbs (TCH) for analgesia after total knee arthroplasty (TKA). Methods: A randomized controlled study of 120 patients undergoing TKA were randomly divided into two groups, 60 in each group, from January 2015 to August 2016. The same basis perioperative analgesia protocol was given to patients of both groups. And local TCH phonophoresis was given to patients of the study group twice per day, from 24 h to 7 d postoperative, while local phonophoresis with only saline was given to patients of the control group. We recorded the data of rest and motion Visual Analogue Pain Scores (VAS), range of motion (ROM) of the knee, HSS scores, the time that the patients received pethidine hydrochloride intramuscular injection, WBC, BUN, Cr test and perioperative complications. Results: A total of 111 patients, 53 in study group and 58 in control group, completed the 3 months follow-up and data was analyzed. The patients of the study group had significantly lower rest and motion pain scores at 48 h, 72 h, 96 h, 7 d postoperative (P<0.05). The ROMS at 48 hours, 72 hours, 96 hours and 7 days post-operation were significantly higher in the study group than in the control group. The average HSS scores in the study group were higher than the control group while the HSS of both groups significantly improved postoperative (P<0.05). The patients of study group received less injections of intramuscular meperidine hydrochloride (P<0.05) and there was no significant difference in WBC, BUN, Cr test and no severe local or systemic complications reported. Conclusions: The results indicated that local TCH phonophoresis was shown to provide effective pain relief and decrease the use of pethidine hydrochloride postoperative. It was also benefit for the rapid early functional recovery in TKA postoperative without severe complications. In summary, local TCH phonophoresis could be considered as a benefit analgesic support in TKA perioperative.

Keywords: Phonophoresis, Traditional Chinese Herb, knee, arthroplasty, analgesia

Introduction

Osteoarthritis (OA) is one of the most common joint diseases in adults all over the world [1]. Total Knee Arthroplasty (TKA) is recommended as the main therapy in end-stage knee osteoarthritis, as well as one of most successful surgery in orthopedics [2]. However, TKA is usually associated with severe postoperative pain [3]. Severe postoperative pain often leads to postoperative rehabilitation exercises delay, joint stiffness and limitation of motion, which have an adverse effect on vital organ function in the long run. Outcomes and satisfaction of the surgery also decrease [4]. Therefore, the therapies aimed to relieve or eliminate pain in the perioperative period of TKA should be given more attention by every joint surgeon [5-7]. Although multiple kinds of methods has been used for analgesia of TKA, the most widely used treatment is oral drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) [8]. But NSAIDs and other drug therapies involve potential hazards including gastrointestinal side effects, particularly in the elderly.

Phonophoresis is a therapeutic method that uses ultrasound to enhance percutaneous absorption of drugs. Phonophoresis with drugs such as NSAIDs and Lidocaine has been reported to treat pain and inflammation in acute joint injury and OA [9, 10]. As a new analgesic therapy, local drug phonophoresis have been reported as a potent and noninvasive analgesic effect when patient taken postoperative rehabilitation exercises [11]. Further, therapy of ultrasound conductance drug regional penetration reduced the complication rate owing to oral or injectable

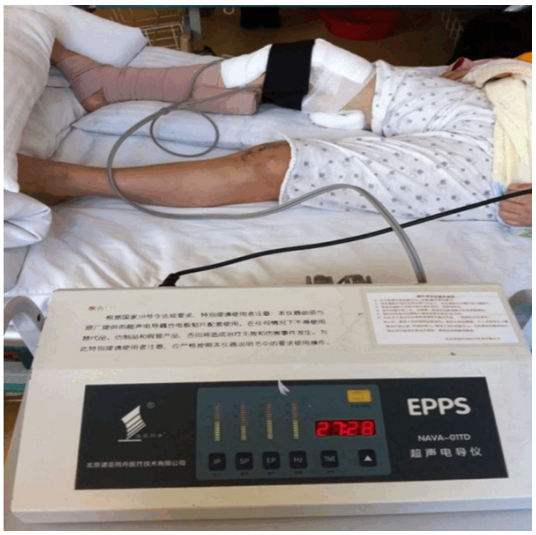

Figure 1. Local TCH phonophoresis machine.

analgesics, which is a beneficial supplement to multimodal analgesia [12]. Traditional Chinese Herb (TCH) has been used for thousands of years to treat various diseases, with many herbal remedies being effective in pain relief [13]. TCH now is playing an more and more important role in the treatment of acute sports injury and chronic joint pain in China [14]. So that it should be effective for pain control when using after TKA. It's a long problem to find an appropriate method that Chinese herbal medicine can play the best effect, especially after surgery, due to the limitation of oral pathway of drugs generally [15]. Phonophoresis is a new choice to maximize the efficacy of TCH just in local areas which leads little side effect on other vital organs. With huge advantages of noninvasiveness, minimal risk of adverse effects associated with systemic administration of drugs, and the combined therapeutic effects of both ultrasound and drugs, local TCH phonophoresis should be the new method for analgesia after TKA. But few scientific evidences can be found to support this method effective when using after TKA. To validate the effectiveness of this method, we conducted this study to evaluate the analgesic effect of local TCH phonophoresis in patients undergoing TKA.

Materials and methods

Research objects

From January 2015 to August 2016, 120 patients with OA who was scheduled eligible for primary unilateral TKA in our department were enrolled. The patients were randomized assigned to study group and control group according to the therapy procedure, 60 patients in each group. The patients of both groups received the same basic analgesic protocol. The patients in study group received local phonophoresis therapy with TCH after TKA while the patients in control group receive local saline phonophoresis as control. The patients should have no mental illness or expression disorders and were not allowed to take analgesic medication less than two weeks prior to surgery. Preoperative laboratory examination of all patients should be almost normal. All surgical procedures were performed by the same orthopedic surgeons. Posterior stabilized knee prosthesis (Wright Medical Technology, Inc. Arlington, US) were chosen, and patellar prosthesis was not chosen. Pneumatic tourniquet was routinely applied during the whole operation until sutured. To prevent deep vein thrombosis, oral rivaroxaban was started in 12 hours after surgery until 2 weeks postoperative. Drainage tubes were applied and were removed 24 hours after operation. Continuous passive motion (CPM) began from then on.

The patients with the following conditions were excluded: (1) Experiencing a longer hospital stays and functional training delayed because of complications; (2) Research programs were changed or terminated due to adverse reactions related to analgesic therapy; (3) Research program were terminated because of individual compliance.

Materials

TCH: Traditional Chinese Herbs (Sanqi Huoxue Tang): Radix notoginseng (Sanqi), 9 g, Sanguis draconis (Xuejie), 6 g, Drynaria fortune (Gusuibu), 12 g, Chinese Polyphaga (Dibiechong), 6 g, native copper (Zirantong) 15 g, and some adjuvants. Each dose of TCH was decocted with 1000 ml water for 1 hour, big fire for 20 minutes and then turned into small fire. The decocted TCH should be used while warm.

Phonophoresis instruments: NAVA-01TD ultrasound conductivity apparatus, NAVA-02 ultrasound conductivity coupling patch (Medical Technology Co, Ltd. Beijing Nava).

Methods

Analgesic protocol: All patients of both two groups received the same basis analgesic pro-

Table 1. Baseline characteristics of patients ($\bar{x}\pm s$)

	Study	Control	*P*
Number of patients	53	58	
Age	67.34±8.82	65.22±10.56	0.256
Sex (Male/Female)	17/36	16/42	0.605
BMI (kg/m^2)	27.87±6.20	26.93±7.0	0.460
Side of TKA (left/right)	28/25	24/34	0.227
Time of operation	82.47±5.50	82.95±5.61	0.650

Table 2. Rest VAS scores ($\bar{x}\pm s$)

	Study	Control	*P*
Pre-operation	5.62±1.63	5.54±1.68	0.800
24 h post-operation	5.85±1.82	6.11±1.34	0.391
48 h post-operation	5.09±0.97	5.85±1.26	0.001
72 h post-operation	3.55±1.66	4.72±1.08	<0.001
96 h post-operation	3.48±1.45	4.59±1.28	<0.001
7 d post-operation	3.07±1.54	3.77±1.22	0.009

tocol. While the study group was given auxiliary ultrasound conductance drug penetration in 24 hours postoperative, 2 times every day. Ultrasound therapy were stopped on 7 days postoperative.

Basis analgesic protocol: All of the patients received no oral or injective analgesics 14 days before surgery, and mixed analgesics containing of 20 mL ropivacaine, 0.5 mg epinephrine, and 20 ml physiological saline were injected around the knee capsule before prosthesis components were installed. In 24 hours postoperative, intravenous injection of 40 mg nepari celecoxib was given within 48 hours. Then, of tramadol hydrochloride sustained-release one tablets (2 times every day) was used between 48 hours and 7 days postoperative. While oral celecoxib 200 mg was given between 48 hours and 6 weeks postoperative. If some patients occurred severe pain, intramuscular pethidine hydrochloride were given.

Operation of phonophoresis instruments: 1) Parameter settings: Hole pulse: square wave 30 mS, Duty cycle 1:1a peakvoltage of 90 V, 6 every group, per minute of one group; ultrasound: 20 kHz, a peak power of 300 mW/cm^2, action area 12 cm^2. Conductance pulse: square wave 2000 HZ, Duty cycle 1:1, 100-Hz sin halfwave, a peak voltage of 40 V, effective current strength 0.2 mA/cm^2. 2) Operation: the coupling electrode patch was installed into emitter tips, 20 mL of TCM liquid was average infused into 2 coupling gel sheets. Posterolateral knee which underwent surgery was selected, while the skin incision was avoided. All patients were required skin clean and intact. After parameter settings, about 30 min per time, head stick containing two Gel patches for treatment was fixed to the head by elastic bandage. Then start the phonophoresis treatment and keep 45 min. All operations were carried out by specialized personnel (**Figure 1**).

Evaluations

The patients who presented with severe postoperative pain (VAS>7 points) were given intramuscular injection of pethidine hydrochloride 50 mg, and the numbers of intramuscular injection were recorded.

Visual analogue scales (VAS) pain score: At rest and 15 minutes after continuous motion, the VAS scores were recorded on preoperative and 24 h, 48 h, 72 h, 7 d postoperatively. Responses clustered into three ranges: 1-3 for mild pain, 4-6 for moderate pain, and 7-10 for severe pain.

The range of motion (ROM) of knee was measured on preoperative and 48 h, 72 h, 96 h, 7 days, 6 weeks, and 3 months postoperatively.

The Hospital for Special Surgery (HSS) knee score were evaluated on preoperative and 2 weeks, 3 months postoperatively.

The White Blood Cell (WBC) count, Blood Urea Nitrogen (BUN) and Serum Creatinine (SCr) were detected on preoperative and on 2 d, 7 d, 14 d postoperatively.

Severe local skin complications directly due to the using of ultrasound were recorded, such as erythra, ulceration or other allergical reaction locally or systematically.

Statistical analysis

Demographics, disease-related characters and outcomes were described with the use of frequencies for categorical variables and the mean and standard deviation for numeric variables. The impact of TCH was examined by rest VAS scores, motion VAS scores and range of motion at different post-operation time points (24 hours, 48 hours, 72 hours, 96 hours and 7 days), with the application of t-tests. *P*-values of 0.05 or less were considered to indicate statis-

Table 3. Motion VAS scores ($\bar{x}$±s)

	Study	Control	*P*
Pre-operation	7.68±1.66	7.55±1.04	0.619
24 h post-operation	7.12±1.85	7.32±1.71	0.555
48 h post-operation	4.76±1.23	6.05±1.31	<0.001
72 h post-operation	4.55±1.35	5.77±1.45	<0.001
96 h post-operation	4.33±0.97	5.05±1.19	<0.001
7 d post-operation	3.98±1.12	4.82±1.09	<0.001

Table 4. Range of motion ($\bar{x}$±s)

	Study	Control	*P*
Pre-operation	81.2±11.5	82.8±12.4	0.484
48 h post-operation	58.5±6.8	47.6±7.7	<0.001
72 h post-operation	77.9±9.2	59.5±8.7	<0.001
96 h post-operation	86.5±10.4	75.8±9.9	<0.001
7 d post-operation	96.6±10.1	90.9±9.3	0.002
6 w post-operation	105.1±10.5	102.8±10.8	0.259
3 m post-operation	106.4±12.2	104.8±13.1	0.508

tical significance. The analysis was performed using SPSS version 20.0.

Results

A total of 111 patients, 53 in study group and 58 in control group, who were not lost to follow-up were analyzed. The age, sex, BMI and time of operation of the two groups have no statistical difference preoperative (P>0.05, **Table 1**).

Preoperatively, knee function score of HSS were (36±6) points and (34±6) points, there was no significant difference for between two groups, (t=1.855, P>0.05); On 3 months postoperative, HSS score for both groups showed a significant increase, (87±11) points verus (81±10) points, while HSS score in study group was significantly more than control group (t=2.747, P<0.05).

The result of VAS scores and motion of the knees between the two groups could be concluded through **Tables 2**, **3**. VAS score: There were no significant differences of the rest and motion pain scores between the two groups preoperative and 24 h postoperative (P>0.05). The patients of the study group had obviously lower rest and motion pain scores at 48 h, 72 h, 96 h, 7 d postoperative (P<0.05). Range of motion (ROM): There were no significant differences of the ROM between the two groups preoperative (P>0.05). While the ROM of the study group was better than the control group at 48 h, 72 h, 96 h, 7 d postoperative (P< 0.05). However, the ROM resumed to the same level at 6 w, 3 months postoperative. (**Tables 2**-**4**).

During hospitalization, the number of intramuscular meperidine hydrochloride in study and control group were 40 and 71 times, respectivelty. It was significantly less in study group (x^2=10.46, P<0.05).

We detected the White Blood Cell, Blood Urea Nitrogen and Serum Creatinine pre- and postoperative, but there was no difference of these data between the two groups (P>0.05).

Although 6 patients who received phonophoresis therapy reported light and temporary flush at the local skin, vanishing soon after changing the position of patch, no severe local or systemic complications were presented in study group.

Discussion

Low-frequency ultrasound-mediated transdermal drugs delivery opened up a new stage of transdermal administration. Pulsed ultrasound with frequency 20 Hz, power less than 2.5 W/cm^2, enhanced tissue penetration, reduced sonic reentry and thermal conversion [9]. Homogeneous cavitation effect and radiation pressure resulted in the establishment of biological pathway penetrated tissues and the kinetic energy of convection and running [16]. Programmed combination of electroporation, ultrasound and phonophoresis produced a synergistic interaction which promoted the formation of specific artificial biological pathways among skin, tissue and cell membranes. With the drive of convective transport and radiation, drugs were infiltrated into lesions though artificial biological pathway, and infiltrated areas with a high drug level produced, which might promote drugs to intracellular transport, and achieve treatment effect. Drug import organizations with a deepest depth of 12 cm and the effective concentration could last 24 h. In addition, bioavailability showed obvious increase with a decrease in amount of medication. According to this study, more than 87% drugs could reach to lesions effectively. Compared to intravenous administration, phonophoresis administration provided similar or higher drug level with target organ stability, and the efficacy

last longer. However, plasma concentration is extremely low which might reduce the systemic first pass effect and adverse reactions. Therefore, the ultrasound administration especially phonophoresis has a good prospect of clinical application [17].

Postoperative pain of TKA leads to rehabilitation exercise delay, hospitalization prolong, and several systemic complications. Postoperative pain are not only associated with bad surgical outcomes and lower patient satisfaction, but also tremendous sense of fear [18]. Therefore, postoperative pain of TKA was a challenge to every surgeon. Preemptive analgesia and multimodal analgesia were gradually recognized as main pain management with increase of surgical cases and accumulation of physician experience [19]. Multimodal analgesia in combination with advanced oral drug, partial closure of knee, a variety of several analgesic drugs by sequential therapy could significantly and safely decrease the perioperative pain, and hospitalization time [20].

Over the past few years, ultrasonic transdermal drug delivery mode especially phonophoresis has been widely used in conservative treatment and physiotherapy [21]. In some surgeries, local anesthetic lidocaine penetrated into peripheral tissues of the knee by low-frequency ultrasound to achieve analgesia effect. Gradually, phonophoresis becoming a therapeutic method that uses ultrasound to enhance percutaneous absorption of drugs [22]. According to this theory, it is useful for the pain control after TKA. In some reports, phonophoresis with NSAIDs has been reported to treat pain and inflammation in many musculoskeletal conditions such as carpal tunnel syndrome, heel pain, myofascial pain, epicondylitis, muscle injury, shoulder pain, and OA [23-29]. Advantages of this method include noninvasiveness, minimal risk of adverse effects associated with systemic administration of drugs, and the combined therapeutic effects of both ultrasound and NSAIDs. But a randomized controlled trial [30] reported that ibuprofen phonophoresis was not superior to conventional US in treating patients with knee OA.

Sanqi Huoxue Tang is an effective pair of traditional Chinese herbs and has been widely used in an acute chronic pain caused by injury and surgery [31]. The main components of these herbs included Radix notoginseng (Sanqi), Sanguis draconis (Xuejie), Drynaria fortunei (Gusuibu), Chinese Polyphaga (Dibiechong), native copper (Zirantong). Radix notoginseng is a kind of bitter plant that relieved stagnation through venting, to promote blood circulation for removing blood stasis, especially in the treatment of acute injury with swelling and pain [32]. Sanguis draconis played important role of decreasing swelling and analgesia [33]. Drynaria fortunei, bitter taste and moderate temperature, can be absorbed into the kidney to cure some orthopeadic diseases [34]. Chinese Polyphaga, with high mobility, mainly penetrated the liver channel to eliminate swelling and relieve pain [35]. Natural copper, which could break accumulation of the gas, was good assistant for eliminating ecchymosis and curing injury [36]. Various herbs played a total role of promoting blood circulation and making the regular channels warm unobstructed, to achieve the goal of repairing damaged tissue, removing rot myogenic and relieving pain. The external application of Chinese medicine could directly promote the local blood circulation and tissue metabolism and reduce tissue spasm adhesion and fibrosis, so that local tissues could get more rapid improvement and recovery as the ischemia and hypoxia symptoms alleviated [37]. Local phonophoresis could improve the absorption efficiency of these Chinese herbs.

After a period of observation and follow-up, we acquired several scientific evidences to support this new method of local TCH phonophoresis in the pain control after TKA. In our research, both of the rest and motion VAS scores of patients in study group on 24 h, 48 h, 96 h, and 7 d postoperative was less than control group, and the numbers of intramuscular injection of pethidine hydrochloride were also less. The result indicated that local TCH phonophoresis not only supplied good analgesia effect at the early phase postoperatively, but also decreased adverse effects induced by intramuscular injection of pethidine hydrochloride. Compared to the control group, the early range of motions of knee for patients in study group were larger. This result suggested good analgesia effect be necessary for rapid postoperative rehabilitation, which had important impact on confidence enhancing for TKA surgery and rehabilitation. But the result indicated that local TCH phonophoresis was benefit only on the early time of function rehabilitation, while there was no sig-

nificant difference in the ROM of knee after 6 weeks postoperatively. HSS score was significantly higher on 3 months postoperative, which showed effective analgesic was still helpful to sequential functional recovery after discharge, raising the degree of satisfaction of this surgery. It was worth to mention that no severe related complications were presented to patients who received local TCH phonophoresis therapy, and the main perioperative laboratory examination did not indicate higher risk versus the control group, which suggested ultrasound therapy had characters of safe and reliable.

The main limitation of this study is the evaluation of short-term outcomes only. We think that data obtained from long-term follow-up studies would be more valuable in evaluating permanent and favorable effects of these therapies. And although traditional Chinese medicine might be a good choice through phonophoresis, but we can not make sure the further mechanism and safety of these herbs.

Conclusion

In summary, local TCH phonophoresis have the advantage of simple operation, no trauma and no pain. It was not only more effective in pain relief with decreased adverse reactions of analgesic, but also get better result of TKA patients with function improvement and increasing confidence. However, local TCH phonophoresis could be considered as an benefit analgesic support in TKA perioperative.

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Disclosure of conflict of interest

None.

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