

Effect of the ‘Li Qi Huo Xue Li Shui Method’ on postoperative pain after total knee arthroplasty: A systematic review and meta-analysis of randomized controlled trial

Hua Li^{1,a}, Mingwan Ge^{1,b}, Juebei Li^{2,c,*}, Lun Liu^{3,d,*}

¹Department of Orthopedics, Tongcheng County Traditional Chinese Medicine Hospital, Tongcheng, Hubei, China

²Postgraduate Department, Huazhong University of Science and Technology, Wuhan, Hubei, China

³Postgraduate Department, Changzhi Medical College, Changzhi, Shanxi, China

^aLihua01199@163.com, ^b13797237581@163.com, ^cjuebei629@163.com, ^dAllenLL118@163.com

*Corresponding author

Keywords: Li Qi Huo Xue Li Shui method; total knee arthroplasty; postoperative pain

Abstract: This meta-analysis mainly investigated the analgesic effect of Li Qi Huo Xue Li Shui method and inducing diuresis after total knee arthroplasty (TKA). We searched major databases, such as Cochrane Library, CNKI, Wanfang, Dutch Medical Literature Database, VIP, Web of Science, PubMed, Medline, etc., and searched each database from the time of establishment of the database to February 2023 for randomized controlled trial (randomized controlled trial) on the effectiveness of Li Qi Huo Xue Li Shui method in treating postoperative pain following total knee arthroplasty. Randomized controlled trial (RCT) on the treatment of postoperative pain after total knee arthroplasty was searched from the databases of VIP, Web of Science, PubMed, Medline, etc., and a quantitative meta-analysis of the literature that met the inclusion criteria was carried out by using the software of RevMan 5.3. The results showed that, for the patients' VAS scores at one and two weeks postoperatively, the use of Li Qi Huo Xue Li Shui method and inducing diuresis was better than that of the conventional analgesia group, which was [MD = -0.67, 95% CI (-1.02, -0.31), P=0.00002] at one week postoperatively, [MD = -0.58, 95% CI (-0.89, -0.27), P=0.00002] at two weeks postoperatively, [MD = -0.58, 95% CI (-0.89, -0.27), P=0.00002] for the HSS scores postoperatively. For the postoperative HSS score, Li Qi Huo Xue Li Shui method was superior to that of the conventional analgesia group [MD = 4.20, 95% CI (2.87, 5.53), P < 0.00001]. For the postoperative knee circumference, Li Qi Huo Xue Li Shui method was superior to that of the conventional analgesia group [MD = -2.24, 95% CI (-2.74, -1.75), P < 0.00001]. Li Qi Huo Xue Li Shui method has significant efficacy in relieving pain after total knee arthroplasty.

Osteoarthritis (OA) is a common chronic degenerative disease, and the prevalence of knee osteoarthritis (KOA) is the highest ^[1]. In China, the prevalence of KOA is 8.1%, and it is higher in women than in men ^[2]. It is a multifactorial disease of the total joints, the etiology of which is still

unclear, and its occurrence may be related to age, obesity, inflammation, trauma and genetic factors^[3]. Clinically, knee pain, activity limitation, dysfunction, joint deformity and even disability are common symptoms, which seriously affects patients' mobility and quality of life. The treatment of KOA mainly includes two major parts: conservative treatment and surgical treatment, and the common conservative treatment includes basic treatment, traditional Chinese medicine and physical therapy, oral non-steroidal anti-inflammatory drug treatment, intra-articular injection and other therapies^[2]. Surgical treatment is mainly applied to middle and advanced stage KOA patients with poor results of conservative treatment^[4-5], and the commonly used surgical procedures include unicompartmental knee arthroplasty (UKA) and total knee arthroplasty (TKA). However, TKA is often associated with moderate to severe pain after surgery due to pain sensitization and various factors, which seriously affects postoperative recovery, patient satisfaction, and overall outcome. Multimodal analgesia is considered an ideal solution for relieving postoperative pain after TKA, including non-pharmacological (e.g., patient education, psychological interventions, ice packs) and pharmacological measures. Traditional Chinese medicine (TCM) has unique knowledge and insights on KOA, which is a disease of co-morbidity of tendon and bone, impotence and paralysis, and belongs to the category of "Bi Zheng", "Gu Wei" and "Jin Lou" in TCM^[1]. Total knee arthroplasty belongs to the category of "Zhe Shang" in traditional Chinese medicine^[3], and its etiology and pathogenesis mainly include stagnation of qi, deficiency of qi and blood stasis. As one of the representative methods of Chinese medicine analgesia, many special therapies, such as acupuncture, auricular acupoint application, oral administration of traditional Chinese medicine or decoction and fumigation, have been widely used for postoperative analgesia in patients with KOA, but its clinical value needs to be further evaluated. The Chinese Guidelines for Perioperative Pain Management in Artificial Total Knee Arthroplasty affirm that auricular acupoint taping and acupuncture have some adjuvant analgesic efficacy, and recommend that they be promoted for use in institutions where they are available to assist in the reduction of early postoperative pain, but there is a lack of evidence related to the use of traditional Chinese medicine for analgesia. Wu and other scholars proposed that the general pathogenesis of Chinese medicine for middle-aged and elderly patients after orthopedic trauma and major surgery is characterized by qi deficiency and blood stasis^[6], and damage to the spleen and stomach, and established the "Yi Qi Huo Xue Jian Pi Method" as the fundamental rule of Chinese medicine, combined with the fact that postoperative swelling of the knee joints of patients with TKA is often accompanied by the urgent treatment of the symptom, and combined with "Li Shui" and "Li Shui" methods. Combined with the fact that postoperative TKA patients often suffer from knee swelling, it is urgent to treat the symptom by combining the method of "diuresis". Therefore, the purpose of this paper is to systematically evaluate the effect of "Li Qi Huo Xue Li Shui method" on postoperative pain after total knee arthroplasty, to provide evidence-based medical evidence for the clinical application of regulating qi, activating blood and promoting water in treating postoperative pain after total knee arthroplasty, and at the same time, to provide ideas for the treatment of postoperative pain after KOA.

1. Materials and methods

1.1. Literature search strategy

The computer was used to search major databases, such as Cochrane Library, CNKI, Wanfang, Holland Medical Literature Database, VIP, Web of Science, PubMed, Medline, etc., and all relevant literature on the treatment of postoperative complications after knee replacement with the method of Li Qi Huo Xue Li Shui was searched from the time of establishment of the databases to February 2023, and all relevant literature on the treatment of postoperative complications after knee replacement with the method of benefiting qi, activating blood and promoting water. The Chinese

search terms included knee replacement, total knee replacement, total knee replacement, total knee arthroplasty, total knee arthroplasty, artificial joint replacement, artificial total knee replacement, artificial total knee replacement, artificial total knee replacement, tonifying qi, benefiting qi, invigorating blood circulation, resolving blood stasis, eliminating blood stasis, promoting collaterals, invigorating collaterals, relaxing tendons, and the English search terms included " arthroplasty, replacement, knee; knee replacement arthroplasty; knee arthroplasty, total; auricular plaster; tonifying qi; promoting blood circulation; detumescence; analgesia pain", the literature search will be based mainly on a combination of both subject and free words.

1.2. Inclusion Criteria

Type of study: (1) RCT on the treatment of postoperative pain after total knee arthroplasty by Li Qi Huo Xue Li Shui method; (2) Subjects: unilateral postoperative TKA patients, aged 60 ~ 80 years; (3) Interventions: control group conventional analgesic program, including self-controlled analgesic pumps and/or oral analgesic medications, etc.; the treatment group in the control group on the basis of the additional embodiment of Li Qi Huo Xue Li Shui method, the treatment of the specific formulas are not limited to the formulas for The main medicines should include qi regulating herbs, such as astragalus, chenpi, etc.; blood activating herbs, such as danshen, peach kernel, etc.; and water-inducing herbs, such as poria cocos, zejiao, etc. (4) Observational indicators: must include visual analog score (VAS) of pain, and at least one of the following: knee function score (HSS), knee mobility ROM, knee circumference (about 10cm above/below the patella in the knee in the straight position), plasma D-dimer, and so on.

1.3. Exclusion Criteria

Exclusion criteria: (1) the intervention contained prescriptions other than those reflecting the method of Li Qi Huo Xue Li Shui; (2) there were significant differences in the baseline data between the studies; (3) duplicated literature; (4) cases had other diseases involving the joint system, such as rheumatologic and immunologic diseases; (5) the time of measurement for the observational indexes did not satisfy the 7-day postoperative period.

1.4. Data extraction and quality evaluation

Two independent researchers independently managed, evaluated and extracted data from the literature screened according to the literature search requirements by utilizing literature management software. The risk of bias assessment method recommended by the Cochrane Assistance Network was used to evaluate the quality of the included literature. The data were extracted from the following sources: title, publication date, authors, sample size, basic characteristics of the study subjects (gender and age), interventions in the experimental group and the control group, treatment period, observational indexes, randomization method used in the literature, concealment of the allocation, and blinding method.

1.5. Statistical analysis

The data were processed and analyzed using RevMan 5.3 software. The effect scales were selected according to the type of data, and the ratio (OR) was used for counting data; the mean difference (MD) was used for measuring data; differences were considered statistically significant when $P < 0.05$. Studies with less heterogeneity ($I^2 < 50\%$) were combined using the fixed-effects model; studies with more heterogeneity ($I^2 > 50\%$) were combined using the random-effects model, and publication

bias was examined when the number of articles was ≥ 10 .

2. Results

2.1. Literature Search Results

Table 1: Basic Characteristics of the Included Literature

Inclusion studies	Type of literature	Number of persons (male/female)	Age	Intervention	treatment duration (day)	Indicators of outcome	
He ^[7] 2022	RCT	36/36	65.92 \pm 6.53	Anti-injury and Anti-Blood Cancer Soup	Conventional basic therapy	7	2,3
Liu ^[8] 2022	RCT	20/20	64.30 \pm 3.56	regulate qi and relax tendons	Conventional basic therapy	14	1,2
Li ^[9] 2021	RCT	45/45	64.22 \pm 3.34	Enriching Qi, Promoting Blood and Circulating Veins Formula	Conventional basic therapy	14	2,8
Guan ^[10] 2021	RCT	35/35	65.88 \pm 5.55	Tang Tang for Body Pain and Evacuation of Blood Stasis	Conventional basic therapy	7	2,4,6,7
Zhu ^[11] 2020	RCT	29/28	65.89 \pm 3.25	Resurrecting Blood and Revitalizing Blood Soup	Conventional basic therapy	7	1,2,8
Chen ^[12] 2020	RCT	35/35	68.90 \pm 4.68	Resurrecting Blood and Revitalizing Blood Soup	Conventional basic therapy	13	2,4,6,7
Yin ^[13] 2020	RCT	30/30	71.90 \pm 4.41	Dan Tao Swelling Drink	Conventional basic therapy	14	1,2
Luo ^[14] 2019	RCT	30/30	67.13 \pm 3.52	Shuji Tang, a decoction of Chinese medicine that relieves tendons and activates blood flow	Conventional basic therapy	14	1,2,3
Zhao ^[15] 2019	RCT	30/30	69.20 \pm 6.327	four-substance decoction	Conventional basic therapy	14	1,2
Sun ^[16] 2018	RCT	20/20	59.7 \pm 6.868	formula for dispelling blood stasis and promoting circulation of channels	Conventional basic therapy	7	1,2,4
Xiong ^[17] 2018	RCT	45/45	70.49 \pm 5.55	Danqi Niu Ren Ba Zhen Tang	Conventional basic therapy	14	1,2,4,6,7
Zhang ^[18] 2018	RCT	45/30	63.5 \pm 4.8	Gui Zhi Fu Ling Pills	Conventional basic therapy	7	2,4
Han ^[19] 2017	RCT	24/24	63.13 \pm 3.00	Formula for promoting blood circulation, inducing diuresis and reducing swelling	Conventional basic therapy	13	1,2,4
Wang ^[20] 2013	RCT	30/30	63.07 \pm 9.50	Tang for Body Pain and Evacuation of Blood Stasis	Conventional basic therapy	7	1,2

Note: Observations: 1 Knee function score (HSS); 2 Pain visual analog score (VAS); 3 Knee mobility ROM; 4 Knee circumference; (Extension position: about 10 cm above/below patella of the knee); 5 Post-operative complication rate; 6 ESR; 7 CRP; 8 D-2 aggregation

After screening after literature search, we finally included 14 papers for the study ^[7-20], totaling 892 patients (flow chart in Figure 1). The control group was conventionally treated with Western medicine, and the experimental group was added with prescription drugs embodying the method of

Li Qi Huo Xue Li Shui method (see Table 1 for details). All the literature described the correct random allocation method. Quality evaluation of the included literature was performed utilizing the risk of bias assessment method, see Figure 2.

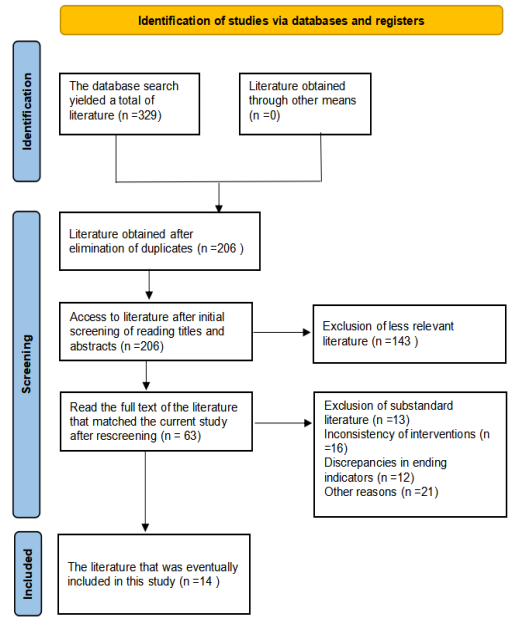


Figure 1: Literature Screening Flowchart

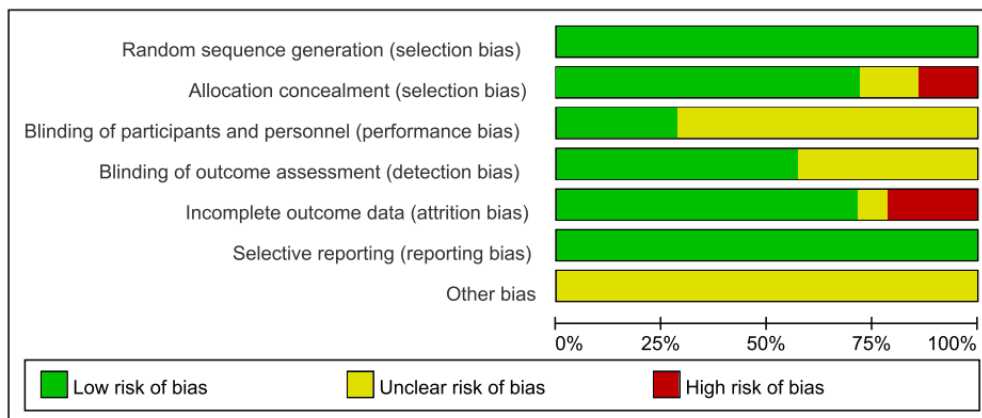


Figure 2: Risk of Bias Assessment Chart

2.2 Meta-analysis results

2.2.1. VAS

All 14 studies reported the VAS score at resting state at 7 days postoperatively, and using a random-effects model ($I^2 = 96\%$, $P < 0.00001$), the treatment group was superior to the control group in terms of improvement in the VAS score at resting state postoperatively [MD = -0.67, 95% CI (-1.02, -0.31), $P=0.00002$]. (Fig 3) Seven studies reported the postoperative 14-day resting-state VAS scores, postoperative 14-day resting-state VAS scores, using a random-effects model ($I^2 = 96\%$, $P < 0.00001$), and the treatment group was superior to the control group in improving the postoperative resting-state VAS scores [MD = -0.58, 95% CI (-0.89, -0.27), $P=0.00002$]. (Fig 4)

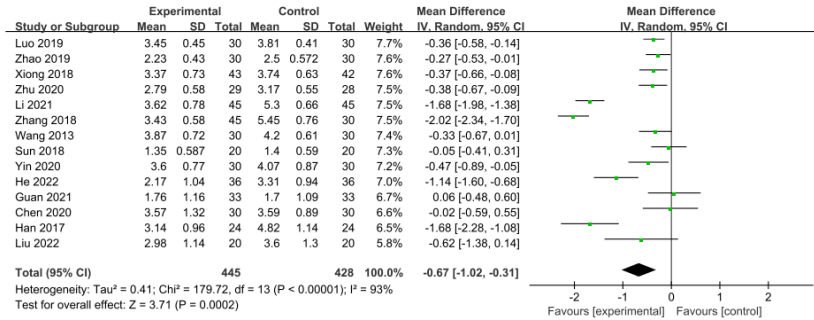


Figure 3:7 days postoperative VAS

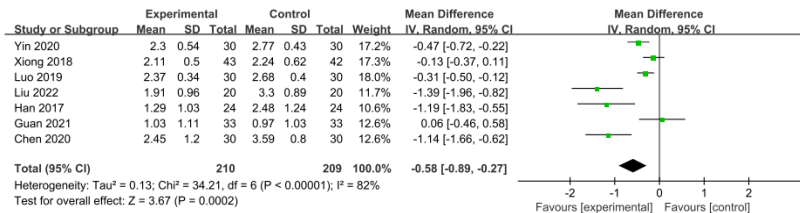


Figure 4: VAS at 14 days postoperatively

2.2.2. HSS

Seven studies reported the postoperative knee function score (HSS) scores, and using a random-effects model ($I^2 = 83\%$, $P < 0.00001$), the HSS scores of the treatment group were superior to those of the control group in terms of improvement of postoperative knee function [MD = 4.20, 95% CI (2.87, 5.53), $P < 0.00001$]. (Fig 5)

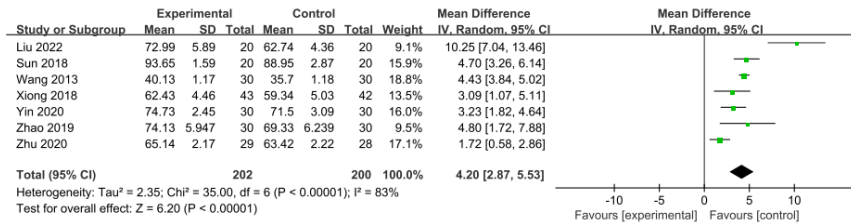


Figure 5: Postoperative HSS

2.2.3. Postoperative knee circumference

Five studies reported postoperative knee circumference, and using a random-effects model ($I^2 = 13\%$, $P = 0.33$), the treatment group's postoperative knee circumference was superior to the control group's in reducing knee swelling [MD = -2.24, 95% CI (-2.74, -1.75), $P < 0.00001$]. (Fig 6)

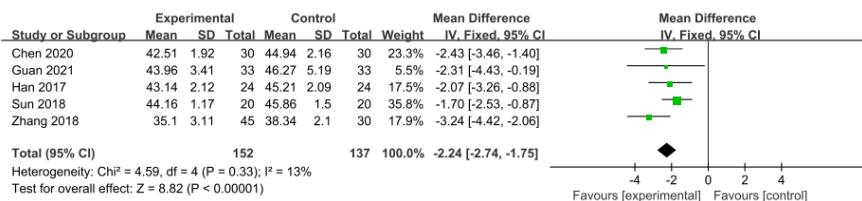


Figure 6: Postoperative knee circumference

2.2.4. Publication bias analysis

A bias test was performed on all the observed indicators, and it was found that the distribution of the funnel plot was basically symmetrical, suggesting that there might not be significant publication bias. (Fig 7).

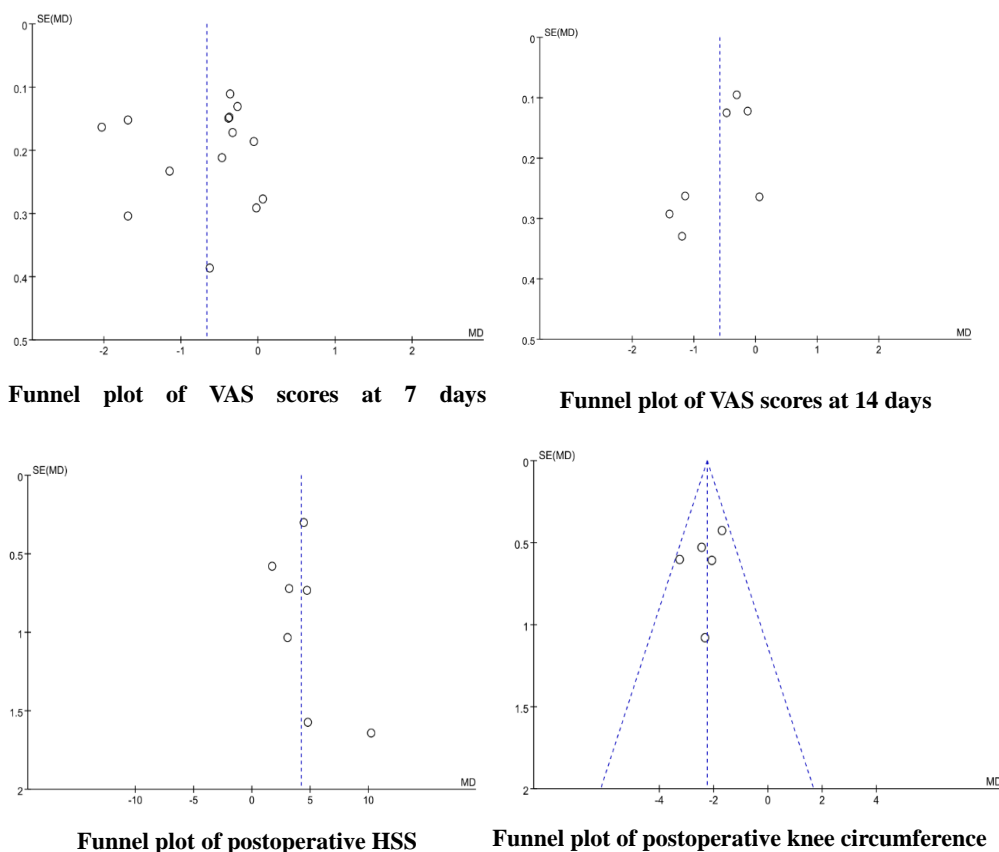


Figure 7: Funnel plot

3. Discussion

Artificial knee replacement belongs to the category of "ZheShang" in Chinese medicine, Chinese medicine in the treatment of injuries not only has a long history, but also good efficacy, injuries are morphology-based disciplines, so the treatment of injuries from the form of qi identification. Suwen yin and yang should be like the book on the pathogenesis of injuries caused by gas injuries and form injuries, swelling and pain, a pithy description: gas injuries pain, form injuries swelling. According to "Pu Ji Fang Fracture Door", "If the limb is fractured due to injury, it will become swollen and distended". When a limb is injured by a gold blade, the blood vessels and meridians are damaged, the blood overflows out of the veins, the path of blood flow is not smooth, and the blood outside the veins stagnates and does not accumulate. Blood overflowing on the surface of the skin is swelling, and blood leaving the veins is stasis. Blood stasis can not only block the veins and qi, but can also cause bleeding again. This is what Chinese medicine refers to as "if you don't get through, you get pain. Combined with modern medicine^[21], the normal tissues of the body are destroyed after TKA, which will inevitably injure the qi and blood, the qi channels and blood veins are blocked, and the stasis is not dispersed, which can be manifested in the limbs as swelling and pain; moreover, most of the patients with KOA are old, with more qi deficiency and blood deficiency^[22]. Therefore, after total knee arthroplasty, qi and blood are damaged again, and the treatment is to regulate qi and relieve pain,

activate blood circulation and eliminate stasis, and promote water retention and swelling, so as to achieve the purpose of Western medicine to improve the blood circulation, reduce swelling and relieve pain. Modern pharmacological studies have confirmed that these herbs have the effect of accelerating local blood flow, improving blood viscosity, anti-inflammatory and analgesic effects, and their use in the treatment of orthopedic-related diseases has achieved recognized results.

The results of this meta-analysis showed that on the basis of the conventional analgesic regimen, the Chinese medicines that Li Qi Huo Xue Li Shui method can enhance the analgesic effect after TKA. There are still some limitations in this study, the quality of the included literature is generally low, related to the fact that most of the literature did not explicitly elaborate the implementation of the blinding method; at the same time, the literature involves study populations from China analgesic pump medication use and the implementation of traditional Chinese medicines in the program of the different, easy to make the outcome indicators caused by the large bias, and it is also an important cause of heterogeneity between the literature. It also increases inter-study heterogeneity, all of which can reduce the reliability of Meta-analysis results. In the later stages of clinical trials^[23], it is necessary to carry out prescription optimization of the formula of the Li Qi Huo Xue Li Shui method and induce diuresis on the basis of diagnosis and treatment. The preferred prescription should be used to conduct a large-sample, multicenter, and multiracial population trial study with high standards and standardization. This can greatly avoid trial bias. Efficient validation of the Chinese medicine method of the Li Qi Huo Xue Li Shui method and inducing diuresis for the treatment of postoperative pain and safety after total knee arthroplasty will provide relevant ideas for clinical treatment.

4. Conclusions

The method of Li Qi Huo Xue Li Shui method to relieve pain after total knee arthroplasty has significant efficacy and can be combined with western medications to have a synergistic effect.

References

- [1] Joint Surgery Group of Orthopaedic Specialized Committee of Beijing Medical Association, Joint Surgery Group of Orthopaedic Branch of Chinese Medical Association. Guidelines on perioperative pain management for total knee arthroplasty in China (2022) [J]. *Journal of Concordant Medicine*, 2022, 13(06): 965-985.
- [2] Zhang Xiaoyun, Zeng Hao, MENG Lin. Progress of pain mechanism and treatment of knee osteoarthritis [J]. *Chinese Journal of Pain Medicine*, 2023, 29(01): 50-58.
- [3] Chen Weiheng. Guidelines for Chinese medicine diagnosis and treatment of osteoarthritis of the knee (2020 edition) [J]. *Chinese Orthopedics*, 2020, 32(10): 1-14.
- [4] Wang Shangquan, Zhu Liguang, Zhan Jiawen, et al. Clinical Practice Guidelines for Rehabilitation in Traditional Chinese Medicine - Osteoarthritis of the Knee [J]. *Journal of Rehabilitation*, 2020, 30(03): 177-182.
- [5] Wang Bo, Yu Nansheng. Expert consensus on step therapy for osteoarthritis of the knee (2018 edition) [J]. *Chinese Journal of Joint Surgery (Electronic Edition)*, 2019, 13(01): 124-130.
- [6] Wu, Guanbao. Clinical and experimental study on the prevention and treatment of lower limb deep vein thrombosis after orthopedic surgery by yi qi, blood activation and spleen strengthening traditional Chinese medicine [D]. Hunan University of Traditional Chinese Medicine, 2008.
- [7] He Guowen, Gao Dawei, Hu Bajun, et al. The effect of Injury Activating Blood Tang on knee joint mobility and pain in total knee replacement patients in the early postoperative period [J]. *Journal of Guangzhou University of Traditional Chinese Medicine*, 2022, 39(07): 1526-1529.
- [8] Liu Zongren, Zhang Mingming, Shi Shujie, et al. Application of the method of regulating qi and relaxing tendons in accelerating rehabilitation after artificial total knee replacement [J]. *Primary Chinese Medicine*, 2022, 1(08): 22-28.
- [9] Li Peng, Liu Rongzhen, Luo Tian, et al. Clinical study on the prevention of deep vein thrombosis after knee arthroplasty with the formula of benefiting qi and activating blood circulation [J]. *New Chinese Medicines and Clinical Pharmacology*, 2021, 32(02): 268-273.
- [10] Guan Siyan. The efficacy of Body Pain and Blood Stasis Tang on the early functional recovery of patients with qi stagnation and blood stasis after total knee arthroplasty [D]. Hunan University of Traditional Chinese Medicine, 2021.
- [11] Zhu YS. Clinical Observation on Swelling and Related Factors of the Affected Limb after Artificial Total Knee

- Arthroplasty by Addition and Subtraction of Fuxing Yuan and Activating Blood Tang [D]. Shandong University of Traditional Chinese Medicine, 2020.
- [12] Chen Yifan. Clinical study on the efficacy of Fuxuanxuibu Tang in treating inflammatory reaction after total knee arthroplasty [D]. Fujian University of Traditional Chinese Medicine, 2020.
- [13] Yin ZY. Clinical observation on the treatment of limb swelling after knee osteoarthritis arthroplasty with Dan-Tao Anti-Swelling Drink [D]. Fujian University of Traditional Chinese Medicine, 2020.
- [14] Luo Tianjie. Clinical observation on early functional rehabilitation after total knee arthroplasty by Shujin and blood activating soup [D]. Fujian University of Traditional Chinese Medicine, 2019.
- [15] Zhao Xiao. Clinical efficacy of Tao Hong Si Wu Tang in treating postoperative swelling and pain after knee arthroplasty based on the concept of "qi injures pain and form injures swelling" [D]. Chengdu University of Traditional Chinese Medicine, 2019.
- [16] Sun Yanzhen. Study on the effect of expelling blood stasis and clearing collaterals formula on pain and rehabilitation of affected limbs after TKA [D]. Shandong University of Traditional Chinese Medicine, 2018.
- [17] Xiong DD. Clinical efficacy observation of Danqi Niu Ren Ba Zhen Tang on early swelling and pain after total knee arthroplasty in the elderly [D]. Fujian University of Traditional Chinese Medicine, 2018.
- [18] Zhang Zhiquan, Lu Mingfeng, Hu Guangbing, et al. Effect of Guizhi Poria Pill on wound erythema, swelling and heat pain after total knee arthroplasty [J]. Henan Traditional Chinese Medicine, 2018, 38(03): 346-349.
- [19] Han Shiding. Effect of blood-activating, water-inducing and swelling-reducing formula on inflammatory response after total knee arthroplasty [D]. Anhui University of Traditional Chinese Medicine, 2017.
- [20] Wang YX. Clinical efficacy observation of body pain and blood stasis expelling soup in treating swelling and pain after total knee arthroplasty [D]. Fujian University of Traditional Chinese Medicine, 2013.
- [21] Liu Bingjie, Wang Zhaoyang, Chen Yanyan, et al. Effect of cocktail therapy combined with accelerated rehabilitation concept on elderly patients after unilateral total knee replacement [J]. Chinese Convalescent Medicine, 2023, 32(03): 298-301.
- [22] Guo Yali, Li Heting, Li Zhihong, et al. Meta-analysis of the effect of auricular acupressure on pain in patients after knee arthroplasty [J]. Hunan Journal of Traditional Chinese Medicine, 2022, 38(07): 126-132.
- [23] Ma Xuezhi, Ma Yong, Guo Yang. Meta-analysis of the efficacy of tonifying the kidney, strengthening the spleen and activating blood in the treatment of postmenopausal osteoporosis [J]. Chinese Journal of Osteoporosis, 2022, 28(04): 527-535.