SOUTH BAYLO UNIVERSITY

Acupuncture on Knee Osteoarthritis:

A Systemic Review and Meta-Analysis

by

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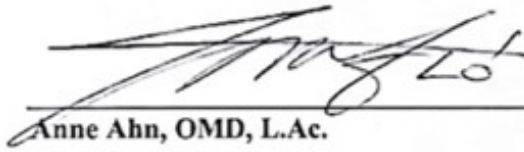

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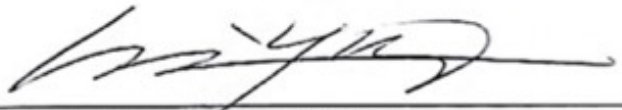

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Research Advisor: Sandjaya Trikadibusana, MD, DAOM, LAc.

ABSTRACT

Osteoarthritis (OA) is a chronic condition characterized by the breakdown of cartilage cause the bone to rub against each other, causing stiffness, pain and loss of movement in the joint. In Traditional Chinese Medicine (TCM), OA is described as Painful Obstruction Syndrome (Bi-Syndrome) indicates pain, soreness, or numbness muscle, tendons, and joint from invasion of eternal Wind, Cold, or Dampness. Acupuncture shows an effective and no side effect for treatment of Bi-Syndrome, includes knee pain due to osteoarthritis. This systematic review and meta-analysis is aiming to evaluate the outcomes of the randomized controlled trials (RCTs) regarding the therapeutic effect of acupuncture on alleviating pain in patient with Knee Osteoarthritis (KOA). The clinical studies included in this review are searched by using the database such as PubMed, Embase, EBSCO, and Google Scholar. The Collected Article are selected according to inclusion an exclusion criteria. The selected RCTs articles are reviewed and analyzed including the involved subjects, method of treatment or intervention, outcomes measurement, statistical analysis, assessment of risk bias and the outcomes. The available data were synthesized in table format, interpreted and summarized from the evidences that support the

effectiveness of the treatment. The 10 eligible studies published between 2011 to 2021, were searched from the electronic databases of PubMed, Embase, EBSCO, and Google Scholar and other relevant sources. The primary outcomes of the review were Visual Analog Scale (VAS) pain score, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), WOMAC success rate score, CPM function, the Time Up & Go (TUG), Range of Motion (ROM), and Lequesne Index score, and the secondary outcomes were adverse effects (AEs) and the relapse rate. Risk Ratio *(RR)* for dichotomous data, mean difference (*MD*) and standardized mean difference (*SMD*) for continuous data were used with associated confidence intervals (*CI*s). VAS pain score [MD -3.94], WOMAC score [SMD -0.44], WOMAC success rate score [RR 0.72], and CPM function [SMD -41.24] showed significant improvement, however, Time Up & Go (TUG) [SMD -0.05] did not show significance. As a conclusion all of the studies found that acupuncture therapy can improve knee osteoarthritis, alleviate joint pain, and improve functional disorder. It is safe and effective treatment for patient with knee osteoarthritis.

Keywords: acupuncture, knee osteoarthritis, pain, randomized controlled trials (RCTs)

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I. INTRODUCTION

Osteoarthritis (OA), the most common form of arthritis, involves the breakdown of joint cartilage and affects an estimated 21 million people in the U.S., according to the American College of Rheumatology. OA most common occurs in the weight bearing joints of the hips, knees, and lower back. It also affects the neck, small finger joints, the base of the thumb and the big toe. OA rarely other joints except when injury or stress is involved.

Nowadays, the primary goals of treating osteoarthritis of knee are to relieve the pain and return mobility. The treatment plan will typically include a combination of the following: 1) weight loss, 2) exercise, 3) pain relievers and anti-inflammatory drugs, includes over-the-counter choices such as acetaminophen (Tylenol), ibuprofen (Advil, Motrin), or naproxen sodium (Aleve), 4) Injection of corticosteroids or hyaluronic acid into knee, 4) alternative therapies include topical cream with capsaicin, acupuncture, or supplements including glucosamine and chondroitin or SAMe, 5) using devices such as braces, 6) physical and occupational therapy, 6) surgery: when other treatments do not work (David Zelman, 2019).

Due to OA will make chronic knee pain and patient has long term using pain medication therefore it increase more side effect. Side effect of Acetaminophen include: nausea, stomach pain, itching, rash, headache, dark urine, and clay-color stool. Ibuprofen also has side effect such as dizziness, stomach and abdominal pain, heartburn, constipation, nausea, rash, ringing in the ears, and swelling. Acupuncture is safe and no side effect, therefore, it considers the first line for alternative treatment.

Studies have shown acupuncture is successful in treating joint pain, including knee OA. In Traditional Chinese Medicine (TCM) theory, chronic knee OA is considered to be mainly due

to kidney deficiency, blood stagnation, and the retention of damp cold in the knee. Acupuncture is excellent for treating osteoarthritis (as well as other types of arthritis). It can reduce symptoms such as swelling, pain, stiffness, and limited range of motion. It can also slow the rate of future degeneration or damage to joints and surrounding tissue.

Objective: The purpose of this study is to evaluate the outcomes of the randomized controlled trials (RCTs) regarding the therapeutic effect of acupuncture on alleviating pain, and improving functional in patient with Knee Osteoarthritis (OA) through the systemic review and meta-analysis.

LITERATURE REVIEW

1. Osteoarthritis in western viewpoints

Definition: Osteoarthritis (OA) is a chronic arthropathy characterized by disruption and potential loss of joint cartilage along with the other joints changes, including bone hypertrophy (Osteophyte formation).

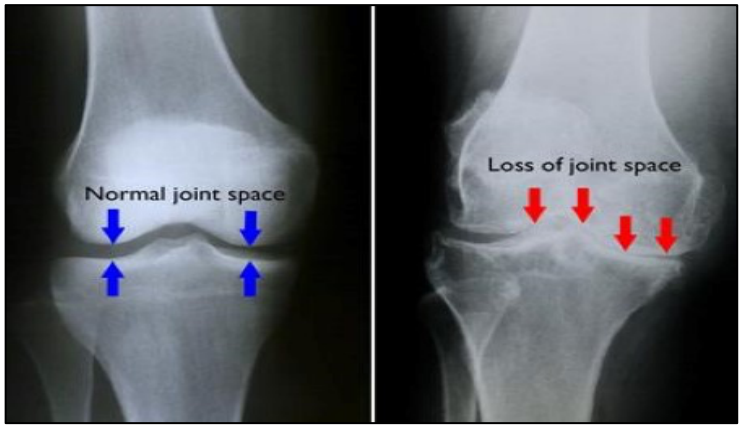

Figure 1. Imaging test of normal knee and arthritis knee.

(Left) In this x-ray of a normal knee, the space between the bones indicates healthy cartilage (arrows). (Right) This x-ray of an arthritic knee shows severe loss of joint space (OrthoInfo, 2021).

Etiology: Knee Osteoarthritis can be primary or secondary, depending on its cause. Primary osteoarthritis is articular degeneration without any apparent underlying cause. Secondary osteoarthritis is the consequence of either an abnormal concentration of force across the joint as with post-traumatic causes or abnormal articular cartilage. Possible cause of secondary Knee Osteoarthritis: obesity, joint hypermobility or instability, previous injury to joint, congenital defects (Physiopedia, 2021).

Pathogenesis: The trigger of OA is most often unknown, but OA sometime begin with tissue damage from mechanical injury (eg, torn meniscus), transmission of inflammatory mediators from the synovium into cartilage, or defects in cartilage metabolism. The tissue damage stimulates chondrocytes to attempt repair, which increase production of proteoglycans and collagen. However, efforts at repair also stimulate the enzymes that degrade cartilage, as well as inflammatory cytokines, with are normally present in small amounts. Inflammatory mediators trigger an inflammatory cycle that further stimulates the chondrocytes and synovial lining cells, eventually breaking down the cartilage. Chondrocytes undergo programmed cell death (apoptosis). Once cartilage is destroyed expose bone become eburnated and sclerotic.

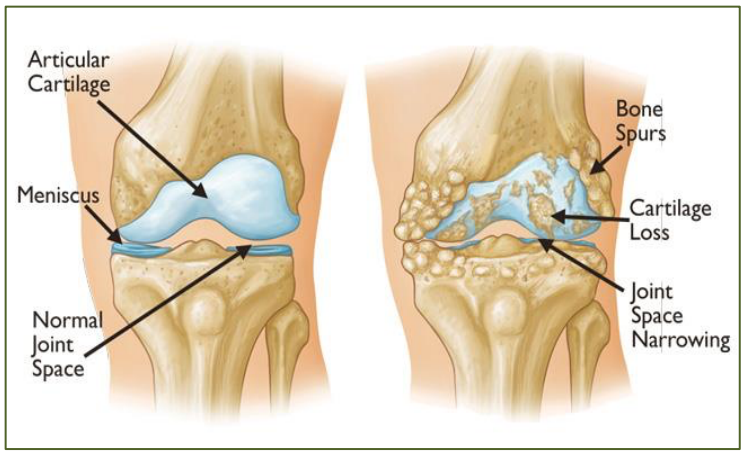

Figure 2. Knee Osteoarthritis.

In osteoarthritis often results in bone rubbing on bone, and produce painful bone spurs due to the cartilage in the knee joint gradually wears away. As the cartilage wears away, it becomes frayed and rough, and the protective space between the bones decreases (OrthoInfo, 2021).

Clinical Manifestations: symptoms of knee osteoarthritis include: pain that increase when active, but gets a little better when rest. Pain is usually worsened by weight bearing, swelling, feeling warmth in the joint, stiffness in the knee, especially in the morning or when sitting for a while. Loss of range of movement, joint enlargement.

Diagnosis: Laboratory studies are normal in OA but may be required to rule out other disorders or to diagnosis an underlying disorder causing secondary OA. If OA is suspected, plain x-rays should be taken of the most symptomatic joints. X-rays generally reveal marginal osteophytes, narrowing of the joint space, increased density of the subchondral bone, subchondral cyst formation, bone remodeling, and joint effusions. Standing x-rays of knee are more sensitive in detecting joint space narrowing.

Treatment: OA treatment goals are relieving pain, maintaining joint flexibility, and optimizing joint and overall function. Primary treatment include physical measures that involve rehabilitation, support device, exercise for strength, flexibility, and endurance, patient education; and modifications in actives of daily living. Adjunctive therapies include drug treatment and surgery.

Complications: Possible complications of OA include: rapid, complete breakdown of cartilage resulting in loose tissue material in the joint (chondrolysis), bone death (osteonecrosis), stress fractures, bleeding inside the joint, infection in the joint, deterioration or rupture of the tendons and ligaments around the joint, pinched nerve (C.S. Mott Children Hospital, 2019).

Prognosis: Osteoarthritis cannot be reversed, however, treatments are available. The primary goals of treating osteoarthritis of the knee are to relieve the pain and return mobility**.** The treatment plan will typically include a combination of the following: weight loss**,** losing

even a small amount of weight, if needed, can significantly decrease knee pain from osteoarthritis. It is also possible that a few simple lifestyle changes can slow its progression and improve your personal prognosis.

According to the American College of Rheumatology, losing just 10 pounds of weight over a 10-year period can reduce the chance of developing OA by up to 50 percent. They also recommend that if patients are overweight and have been diagnosed with OA, daily exercise to keep and build strength and other weight-loss strategies can help take the pressure off the joints. In addition, it is recommended that limit the amount of work the affected joints do. Simple things like raising the height of chairs you sit in and reducing the number of repetitive motions the joint does can make a significant impact. Assistive devices like walking with a cane can also improve the level of pain you feel (Very Well Health, 2021).

2. Osteoarthritis in TCM viewpoints

Definition: In TCM, osteoarthritis is categorized as a Bi (pronounced "bee") syndrome. According to TCM, Bi syndromes are typically caused by a combination of cold, dampness and wind. Bi syndromes are disorders that occur due to obstruction of the energetic meridians or pathways. The Qi (pronounced "chee"), is also known as the energy or life force, tends to become blocked due to swelling or immobilization of the joint. Also a lack of blood circulation may oftentimes be a contributing factor.

Etiology: Invasion of external pathogenic factors such as Wind, Cold or Dampness is by definition the main cause of Painful Obstruction Syndrome. Another cause included excessive physical exercise, overwork, childbirth, trauma, and emotional stress.

Pathogenesis: Painful Obstruction Syndrome is by definition an affliction of the channels alone, not the internal organs. However, in chronic Painful Obstruction Syndrome and in the elderly, internal factors (deficiency of Qi and Blood) are important contributory factors to the development of the disease. In chronic Painful Obstruction Syndrome; Phlegm and Blood stasis are two important internal pathogenic factors. Deficiency of Liver and Kidneys, and degeneration of sinews (cartilages) and bone, autoimmune disease are also cause of chronic Bi Syndrome (Giovanni Maciocia, 2008).

Clinical Manifestations: The symptoms that may be present in chronic Painful Obstruction Syndrome are: A general deficiency of Qi and Blood: muscle weakness; Phlegm in the joints: bone deformities; Stasis of Blood: intense pain, rigidity of point, pain worse at night; Deficiency of Liver and Kidneys: malnourishment of sinews (ache and stiffness) and bones (bone and cartilage degeneration).

Diagnosis and Treatment: Five types of Painful Obstruction Syndrome; Wind Painful Obstruction syndrome: pain moving from joint to joint; Damp Painful Obstruction Syndrome: fixed pain with soreness, heaviness, numbness and swelling of joints; Cold Painful Obstruction Syndrome: severe pain in one joint; Bony Painful Obstruction Syndrome: painful joints with swelling and bone deformities. Treatment principle is aimed at expelling Wind, scattering Cold and resolving Dampness. It is necessary to expel all three pathogenic factors simultaneously. Nourish Blood to expel Wind. Tonifying Fire to scatter Cold. Tonify Qi to resolve Dampness.

Complications: The main complication with OA is pain and stiffness in the joints that worsens over time. It's typically most uncomfortable when patients wake up in the morning. Patients might not be able to move joints as freely as they could in the past, and patients may notice a scraping or crunching feeling when they do. Doctors call this crepitus.

Prognosis: The prognosis in patients with osteoarthritis depends on the joints involved and on the severity of the condition. Many times those who suffer from osteoarthritis also need some nutritional counseling and weight management training. Even five extra pounds can create excess stress on the joints. And as demonstrated in the research study, acupuncture can be an excellent addition for the management of symptoms associated with knee osteoarthritis. By making positive changes and including acupuncture treatments, osteoarthritis sufferers can effectively manage this debilitating disease.

3. Research Studies on the prospective benefits of acupuncture in the treatment of osteoarthritis in brief

There are many studies shows that acupuncture is effective treatment for the knee pain due to osteoarthritis (Bi-Syndrome).

Scharf H-P and other (2006), studied Acupuncture and osteoarthritis-a three–armed randomized trial to assess the efficiency and safety of traditional Chinese acupuncture (TCA) compare with sham acupuncture and conservative therapy in patients with chronic pain due to osteoarthritis of the knee. A randomized, controlled trail was carried out at 315 primary care practices staffed by 320 practitioners with at least 2 years' experience in acupuncture. 1,007 patients participated who had had chronic pain for at least 6 months due to osteoarthritis of the knee. The intervention were: up to 6 physiotherapy sessions and as-needed anti-inflammatory drugs plus 10 sessions of TCM; or 10 session of sham acupuncture; or 10 physician visits within

6 weeks. The results found that the success rates were 53.1% for TCA, 51.0% for sham acupuncture, and 29.1% for conservative therapy. Acupuncture groups had higher success rates than conservative therapy groups (relative risk for TCA compare with conservative therapy 1.75, relative risk for sham acupuncture compared with conservative therapy 1.73). There was no difference between TCA and sham acupuncture (relative risk, 1.01).

The University of Maryland studied 570 patients with knee osteoarthritis (Mariada Hitti, 2004). The knee osteoarthritis patients were randomly assigned to receive either 23 sessions of traditional Chinese acupuncture, 23 treatments of sham acupuncture, or a 12-week knee osteoarthritis education course. In the sham acupuncture group, guide tubes were tapped at two points on the abdomen but no actual acupuncture was given. At the end of the 26-week study, they had the greatest decrease in knee osteoarthritis pain and the biggest improvement in knee osteoarthritis function. The result show that Traditional Chinese acupuncture is "effective" at reducing knee osteoarthritis pain and improving function in people with knee osteoarthritis.

II. MATERIALS AND METHOD

A. Types of studies:

The study type is a systemic review and meta-analysis using evidence from literature to summarize critical aspects of knee osteoarthritis. The search terms “acupuncture”, “pain”, “knee osteoarthritis”, and “randomized control trial” was used. The systemic review and meta-analysis was limited to randomized control trail (RTCs) with clear hypotheses, objectives, setting, participants, assessments, interventions, outcome, and conclusion.

B. Search Strategy

1. Collecting:

The electronic search strategy was conducted from database such as PubMed, Embase, EBSCO, and Google Scholar. The Collected Article is selected according to inclusion an exclusion criteria. The timeframe for the publication of article was set from 2011 to 2021. The searches were included all accessible article that were published in English language.

2. Inclusion Criteria:

- Clinical Studies, Human Studies
- Randomized Controlled Trials (RCTs)
- Year of publications: 2011 to 2021
- English language
- Participants must be diagnosed with knee osteoarthritis
- Acupuncture with/without electro-stimulation
- Full texts are available

3. Exclusion Criteria:

- Non-Randomized Controlled Trials
- Case study, case series, survey, cohort study
- Animal Studies
- Moxa, Cupping
- Acupressure, TuiNa, Scrapping
- Chinese Herbs
- Language other than English

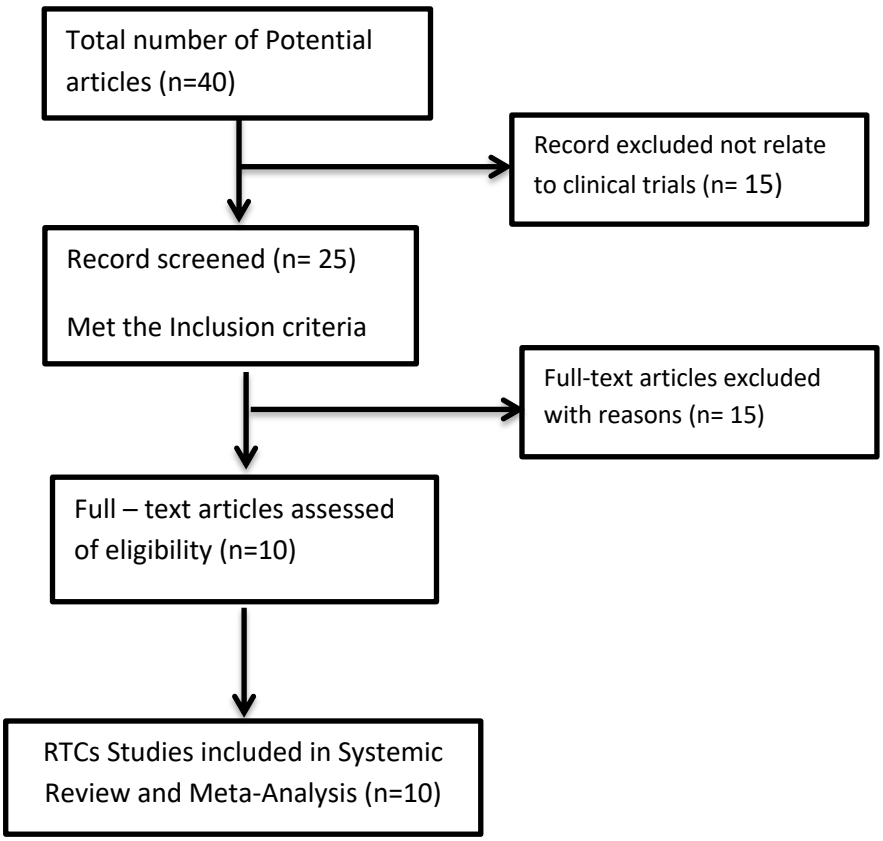

Figure 3. Flow diagram of study selection process

4. Data Analysis:

The characteristics of the RCTs on Knee Osteoarthritis included in this review were analyzed and summarized by the order of Author and Year, Sample Size and Subject Data, Research Methods, P-Values and Outcome.

5. Data Extraction and Conversion

Following the P-I-C-O method, information of Literature Information, Methods, Participants, Interventions and Outcomes were extracted from each study and summarized as a tables.

1) Data extraction items

Extracting data for systematic review and meta-analysis from selected literature research information include: literature information, methods, participants and intervention, outcomes and others. as shown in Table 4.

2) Conversion of data

Mean value, median difference, standard mean deviation, standard error, odds ratio, relative risk of the extracted data. Quantitative results of the same concept were derived by checking the basic values of Meta-analysis. The mean difference and 95% CI (confidence interval) value of the change, values of the intervention group, and the control group are used as default value and entered into Cochrane Collaboration's Review Manager 5.4 (RevMan 5.4).

6. Assessment of Risk of Bias (RoB)

Bias in the randomized comparative clinical trial literature selected for systematic review. For risk assessment, use the RoB (Risk of Bias) software provided by RevMan 5.4. The risk of bias when conducting systematic reviews and meta-analyses that to be extracted from the literature and the evaluation criteria are: Random sequence generation, Allocation concealment, Blinding of participants and personnel, Blinding of outcome assessment, incomplete outcome data, and Selective reporting.

7. Heterogeneity Assessment

The level of heterogeneity across the studies was estimated by overlapping CI in forest plots, and the value of the I^2 statistics for heterogeneity test and the chi-squared test for statistical heterogeneity. P value <0.05 were considered to indicate statistical significance in all the results. The analysis of the effective treatment was performed in the meta-analysis using the RevMan 5.4, the outcome of fourteen subgroups in the ten documents, was meta-analyzed and shown as a forest plot. (Figure 6-12)

Higgins's I^2 statistics 30

To quantify inconsistencies, Higgins's I^2 statistics was used. The degree of heterogeneity was depended on the $I^{2\cdot}$.

The criteria are as follows in order to analyze the heterogeneity.

$0\% \leq I^2 \leq 40\%$: may not be significant heterogeneity

$30\% \leq I^2 \leq 60\%$: may be moderate heterogeneity

$50\% \leq I^2 \leq 90\%$: may be substantially heterogeneity

$75\% \leq I^2 \leq 100\%$: significant heterogeneity

8. Reporting Bias Assessment

In order to identified bias such as publication bias, time lag bias, multiple publication bias, location bias, citation, reporting bias, language bias, and outcome reporting bias, the funnel plot was attained by Review Manager 5.4 for preventing the overestimation of summary estimates in the effectiveness of the treatment.

9. Meta-Analysis

Meta-Analysis Outcome measures for the analysis of the review were VAS pain score, WOMAC score, WOMAC success rate score, CMP function, Time Up & Go (TUG), ROM, and Lequesne Index score by using the RevMan 5.4. The outcome of 14 subgroups in the 10 documents was meta-analyzed and shown as a forest plot. (Figure 6-12). All of the data in the review were continuous, and end-point scores were expressed as SMDs for different scales with associated 95% Cl.

II. RESULTS

1. Characteristics of the RCTs on Knee Osteoarthritis Used in This Review

I selected the research target literature from 2011 to 2021, a study of acupuncture on knee osteoarthritis. Electronic database search for randomized comparative group research papers, review of related research references, I was able to secure a total of 40 documents.

Read the original text, such as title, summary, and body of these 40 papers, and either.

After excluding 30 unrelated documents, a total of 10 clinical papers were secured.

Through qualitative evaluation (risk of bias evaluation), 10 randomized comparative research papers were obtained and it was used for quantitative evaluation (meta-analysis).

As shown in Figure 3 and 4, 10 eligible studies were screened and selected for the further steps of meta-analysis. The Characteristics of the 10 RCTs selected for this review are summarized in Table 1.

Table 1. Characteristics of the RCTs on Knee Osteoarthritis Used in This Review

Author and Year	Sample Size and Subject Data	Research Methods	P-Values	Results
1. Max Karner et al (2012)	• N= 116 (no dropout) • Mean age: 62.4 years, range = 40-83 years, with osteoarthritis of the knee, with no history of : Congenital or traumatic deformation of knee, malignant disease, autoimmune disorders, surgery or arthroscopy during the past 12 months, medication with steroids, physical therapy, or acupuncture within the last 4 weeks, intake of opioids during the study period.	• Double-Blinded, RCTs • 1) Classical Acupuncture (CA) 2) Modern Acupuncture (MA) 3) Sham Acupuncture (SA) • Only one knee was treated. Ear and hand acupuncture was not allowed. 10 $\pm$ 2 points were allows • Needles were withdrawn after 30 mins. Acup, 1x3 wk, and 1 wk follow up. • Outcome: Knee Flexibility (ROM), WOMAC	• Classical Acupuncture: significantly relief the pain immediately after needles ($P < 0.001$) • Knee flexibility improvement significantly in classical acupuncture ($P<0.001$)	• All methods achieved pain relief, with a 73% for classical acupuncture, 64% for modern acupuncture, and 48% for sham acupuncture. • Knee flexibility improvement was significant higher after classical acupuncture (10.3 degree; 95% CI 8.9 to 11.7).

Table 1. Characteristics of the RCTs on Knee Osteoarthritis Used in This Review (Continued)

Author and Year	Sample Size and Subject Data	Research Methods	P-Values	Results
2. Qi Wang et al (2020)	• N= 30 (3 dropouts) • Mean age: 63.5 (Electro acupuncture), 65.2 (Sham acupuncture) • Range age = 45-75 years • Both genders, with unilateral or bilateral KOA, diagnosed within 6 months, knee pain, P/L 4/10 or more in last week. • Exclusion: knee surgery, severe effusion on the joint, infection, tumor, trauma, gout	• Single-Blinded, RCTs • Electronic acupuncture (EA) versus Sham Electronic acupuncture (SA) • Patients of each group received 3 sessions weekly for 8 weeks (one session every other week). Each session was 30 minutes. • 8 acupoints and 3 adjunct acupoints for electronic acupuncture group • Outcome: Proportion of responders, TUG, ROM, Lequesne index	• Primary outcome: Electroacupuncture group: 53.3% (n=8), sham electroacupuncture group: 26.7% (n=4); P=0.264) • Secondary outcome: AROM: P=0.024 PROM: P=0.029	• Primary outcome: The proportion of responders in electro acupuncture group at week 8th were twice as much as that in sham acupuncture group with no statistically significant difference. • Secondary outcome: Significant improve from baseline in electro acupuncture group

Table 1. Characteristics of the RCTs on Knee Osteoarthritis Used in This Review (Continued)

Author and Year	Sample Size and Subject Data	Research Methods	P-Values	Results
3. Song Wei et al (2013)	• N= 90 (11 dropouts) • Mean age: 70 years, both genders, with KOA, at least 6 months duration, knee pain, moderate to severe pain, and use of analgesics for at least 1 month. • Exclusion: intra-articular corticosteroid injection into the knee within 4 weeks, severe and unstable chronic illness, CHF, CRF, tumors in knee, autoimmune disease.	• Double-Blinded, RCTs • 1) Meridian-Sinew Release group 2) Acupuncture group 3) Control group: Patients were given conventional drug therapy. • Treatment was 30 mins, 3 x 4 weeks, in acupuncture group and 1x3 wks for meridian-sinew group. Follow up 12 wks. • Outcome : VAS WOMAC	• In the meridian-sinew release group, change in the primary end point of pain at week 12 were significantly greater than in acupuncture group or control group (P=0.041 and P=0.028, resp.) (P < 0.05)	• The meridian-sinew release therapy was show to be more effective than either routine acupuncture or routine drug therapy for the alleviation of pain and improvement of physical function.

Table 1. Characteristics of the RCTs on Knee Osteoarthritis Used in This Review (Continued)

Author and Year	Sample Size and Subject Data	Research Methods	P-Values	Results
4. Zhang Lele et al (2019)	• N= 90 (no dropout) • Mean age: 55.2± 6.0 years, both genders, with KOA, including radiographic visual analogue scale for most day during the previous month, and willing to sign the consent form. • Exclusion: adverse reaction to acupuncture, severe cardiovascular, rheumatoid arthritis, gouty arthritis, pregnant, mental disease	• Single-Blinded, RCTs • Randomized, controlled, three - arm trail 1) Acupuncture (AP) + Usual care (UC) 3) Electroacupuncture (EA) + Usual Care (UC) • 3) Usual care (UC) • Therapy treatment was 2 weeks, 5 sessions /week • Outcome evaluation indicator was VAS WOMAC version 3.1	• At the extension of the treatment period, the pain VAS score of all 3 groups improved gradually compared with each baseline ($P<0.05$). • WOMAC score in the three groups decrease significantly ($P<0.05$)	• During the treatment from 1st to 2nd week, the pain score of the AP+UC and EA+UC groups were less than that of the UC group. • After the treatment for one week or longer, the WOMAC score in the three groups decrease significantly.

Table 1. Characteristics of the RCTs on Knee Osteoarthritis Used in This Review (Continued)

Author and Year	Sample Size and Subject Data	Research Methods	P-Values	Results

5. Pengli Jia et al (2016)	• N= 36 (8 dropouts)
	• Mean age: 56.5 years (range 45 to 75), both genders, with KOA base on pain for most day in the past month, joint space narrowing, clear viscous synovial fluid, morning stiffness less than 30 minutes, bone sound exists.
	• Exclusion: skeletal disorder, sprain or trauma, unable to walk, mental disorder, cardiovascular disease, DM
		• Single-Blinded, RCTs
		• 1) Acupuncture at high sensitized points group
		2) Acupuncture at low/ non sensitized points group
		• Treatment was 30 mins, 3 sessions x 4 wks, Follow up at 8^{th}, 12^{th}, and 16^{th} week.
		• Outcome evaluation:
		  • Primary : Retention rate
		  • Secondary : WOMAC , SF-12
			• Significant change over the time for WOMAC total score and subscales ($P<0.01$), but the group by time interactions were not significant ($P>0.01$).
			• Significant changes over time for SF-12 ($P<0.001$)
				• Primary outcome: Retention rates were similar between the treatment groups, 14(77.8%) patients in the high sensitization group completed 16 week follow-up and compare to 14 (77.8%) patients in the low/non sensitization group.

Table 1. Characteristics of the RCTs on Knee Osteoarthritis Used in This Review (Continued)

Author and Year	Sample Size and Subject Data	Research Methods	P-Values	Results

6. Yan Zhang et al (2016)	• N= 100 (6 dropouts)
	• Mean age: 54.38±8.5 years (range 30 to 80), both genders, with KOA
	• Exclusion: 1) acute knee injury, 2) had ever had hormone or injection in articulation cavity, 3) had oral medicine physiotherapy, acupuncture, or massage in the past 3 months, 4) pacemaker or any metal object in the body, 5) severe disease, 6) pregnant
		• Single-Blinded, RCTs
		• Electro-acupuncture versus Physiotherapy.
		• Acupuncture treatment was 4 weeks, 3 sessions /week, 20 minutes each time.
		• Physiotherapy treatment 5 times a week for 4 weeks, and 30 minutes each time.
		• Outcome evaluation:
		  • WOMAC scoring
		  • MRI scanning: T2 values
			• For acupuncture group, scores of total WOMAC and three subscale for pain, stiffness, and physical function on 4th weekend were significantly lower than those of the physiotherapy group ($p<0.01$ and $P<0.05$)	• Acupuncture show clinical effective on knee osteoarthritis which is superior compared with physiotherapy.
				• Acupuncture show an impact on T2 value in cartilage, which superior clinical effect when compared with physiotherapy.

Table 1. Characteristics of the RCTs on Knee Osteoarthritis Used in This Review (Continued)

Author and Year	Sample Size and Subject Data	Research Methods	P-Values	Results
7. Tain-Qi Wang et al (2019)	• N= 60 (6 dropouts) • Mean age: 58.89±6.75 years (range 47 to 75), both genders, with KOA more than 6 months, VAS intensity ≥ 40 on a 100 point. • Exclusion: knee surgery, floating cartilage, joint effusion or inflammation, malignant or autoimmune disease, pregnant, breast feeding, serious disease or mental disorders.	• Double-Blinded, RCTs • Electro-acupuncture (EA) vs. Manual acupuncture (MA) • EA group were treat with 6-7 local acupoints, or Ashi point, and 2 or 3 distal pts. • MA group has same schedule with EA except that the electrical apparatus • Treatment 24 sessions x 8 wks, and follow 8 wks. • Outcome: WOMAC , VAS	• After 8 weeks of treatment, the response rate from baseline in WOMAC, neither analysis showed a statistically significant difference in the response rate between the two groups (P>0.05).	• EA treatment for 8 weeks was no more effective than MA at reducing the pain, stiffness, and physical dysfunction associated with KOA. • Both EA and MA intervention are feasible and appear safe for patient with KOA.

Table 1. Characteristics of the RCTs on Knee Osteoarthritis Used in This Review (Continued)

Author and Year	Sample Size and Subject Data	Research Methods	P-Values	Results
8. Zheng-Tao Lv et al (2019)	• N= 271 (21 dropouts) • Mean age: 64.6±10.2 years (range 50 years or older), both genders, who met the criteria for KOA formulated by the American College of Rheumatology (ACR). • Exclusion: adverse reactions to acupuncture, severe disease, rheumatoid arthritis, gouty arthritis, pregnant, lactating, mental disease.	• Multicenter, three – arm parallel, RCTs, Sigle-Blinded • Compare the efficiency of two group of Electro-acupuncture (EA): weak EA and strong EA with sham EA. • The treatment for both EA group and sham EA group, 30 mins/session over 2 wks • Outcome: CMP, VAS, WOMAC, NPRS, ES, PPI	• The CMP function score was observed in the strong EA group than in the sham EA group ($P<0.01$) and in the weak EA group vs. sham EA group ($P<0.01$). • The WOMAC, NPRs, ES, and PPI were significantly lower in two true EA groups than sham EA group ($P<0.01$)	• The participants with KOA who received strong and weak EA had significantly improved VAS, WOMAC, NPRS, ES, and PPI but not CMP after 1 week of the treatment than those who received sham EA.

Table 1. Characteristics of the RCTs on Knee Osteoarthritis Used in This Review (Continued)

Author and Year	Sample Size and Subject Data	Research Methods	P-Values	Results
9. LX Chen et al (2013)	• N= 214 (33 dropouts) • Mean age: 60±11.1 years (range 40 years or older), both genders, with KOA for more than 6 months, and moderate pain >4/10 for more than 5 out of 7 consecutive days the week before enrollment. • Exclusion: rheumatoid arthritis, gouty, trauma, neurologic, cardiac or psychiatric disease, pregnant, coagulopathy.	• Double - blind, RCTs • 1) Exercise-base Physical Therapy (EPT) + Acupuncture 2) Non-penetrating acupuncture + EPT • The treatment group received 1 or 2 sessions a week x 12 wks, follow up 26th wks. • Outcome evaluation: WOMAC, BPI Average Pain, SF-36	• Both treatment groups showed improvement from combined therapy with no difference between true (31.6%) and non-penetrating acupuncture (30.3%) in WOMAC response rate (P=0.5)	• At the end of intervention, 74% of patients considered their knee OA symptoms to be at least slightly better, 38% at least better, and 13% much better. No outcomes differed at any intervention of evaluation.

Table 1. Characteristics of the RCTs on Knee Osteoarthritis Used in This Review (Continued)

Author and Year	Sample Size and Subject Data	Research Methods	P-Values	Results
10. Yaun-Shi Liu et al (2013)	• N= 192 (8 dropouts) • Aged: 40-65 years, both genders, met the diagnostic criteria for KOA, signed informed consent. • Exclusion: did not meet the diagnostic criteria for KOA, serious cardio cerebrovascular system diseases, unwilling to accept the treatment. • Suspension : inability to complete the treatment, not complying with treatment protocol, serious complication	• A multicenter, RCTs • 1) Long round needle therapy group (EG) 2) Control group (CG): Ibuprofen (Fenbid) • EG: received the long round needle therapy once every 7 days for 3 therapy session. • CG: received 1 pill each time, twice daily for 3 wks • Follow up 3 months. • Outcome: Therapeutic Effectiveness Index	• The curative effect in EG after both the treatment and the 3 mounts follow up were significantly more superior than that in CG ($P<0.01$).	• In EG, treatment resulted in a basic cure for 79 Pts., was effective for 15 Pts, and was ineffective for 1 Pt. • In CG: treatment resulted in a basic cure for 30 Pts, was effective for 38 Pts, and was ineffective for 11 Pts.

Table 2. Three studies that indicate the best, moderate and weak studied.

Study ID	Sample Size	Research Methods	Results	Note
1. Zheng Tao (2019)	N= 271 (21 dropouts)	Electro-acupuncture (EA): Weak EA, Strong EA, Sham EA 30 mins, 1X 2 wks Outcome: CMP, VAS, WOMAC, NPRS, ES, PPI	Strong and weak EA had significantly improved VAS, WOMAC, NPRS, ES, and PPI but not CMP after 1 week of the treatment than those who received sham EA. (P<0.01)	**The Best:** Large sample size, clear method-three arm parallel, intervention, and clear result
2. LX Chen (2013)	N= 214 (33 dropouts)	1) Exercise-base Physical Therapy (EPT) + Acupuncture 2) Non-penetrating acupuncture + EPT 1 or 2 sessions x12 wks, follow up 26th wks. WOMAC, BPI Average Pain, SF-36	Improvement from combined therapy with no difference between true (31.6%) and non-penetrating acupuncture (30.3%) in WOMAC response rate (P=0.5)	**Moderate:** Large sample size, clear intervention, and clear result
3. Tian Qi Wang (2019)	N= 60 (6 dropouts)	Electro-acupuncture (EA) vs. Manual acupuncture (MA) 3 x 8 wks, and follow up 16th wks. WOMAC , VAS	EA treatment for 8 weeks was no more effective than MA at reducing the pain, stiffness, and physical dysfunction (P>0.05)	**Weak:** small sample size, and similar in intervention

Table 3. Result of the Study

Study ID	No Change	Improved	Effective
1. Max Karner (2012)	-	Knee flexibility improved	All method (CA, MA, SA) achieved pain relief
2. Qi Wang (2020)	-	Responder proportion, TUG, ROM, Lequesne index improved from base line in electro acupuncture group.	-
3. Song Wei (2013)	-	Physical function improved	The meridian sinew release therapy was show effective than routine acupuncture and drug therapy group.
4. Zhang Lele (2019)	-	During the treatment 1st and 2nd wks, VAS pain score was less	WOMAC score was decrease significantly after treatment for 1 week or longer
5. Pengli Jia (2016)	Retention rates were similar between 2 groups	-	Significantly change in WOMAC total score and SF-12
6. Yan Zhang (2016)	-	-	Clinical effective, WOMAC total and three subscales were significantly lower.
7. Tain-Qi Wang (2019)	EA was no effective than MA at reduce the pain, stiffness, and physical dysfunctions.	-	-
8. Zheng-Tao Lv (2019)	CPM was no change in both group	WOMAC, NPRs, ES, and PPI improved in true EA than sham EA group.	-
9. LX Chen (2013)	-	Both treatment groups shown improvement in WOMAC response rate.	-
10.Yaun-Shi Liu (2013)	-	The curative effect in EG more superior than CG	-

2. Data Extraction and Conversion

1) Data extraction items

Extracting data for systematic review and meta-analysis from selected literature, Research information, research methods, research subjects, comparative interventions, results and others as shown in Table 4, were extracted according to the P-I-C-O method.

2) Conversion of outcome data

Among the result data for each item extracted from the selected 10 documents, the clinical significance basic values such as mean value, median value, standard deviation, standard error, odds ratio, ,relative risk from the extracted data were derived comparing the value. The Cochrane Man Review 5.4 (RevMan 5.4) was applied in this meta-analysis using the standard mean difference (SMD) and the 95% confidence interval (CI) in the experiment group and control group.

Table 4. Data Items Being Extracted from the Selected Literature

Data Component	Data Item
Literature Information	Max Karner et al 2012a
Methods	RCT Cross-over, Double blinded
Participants	116 participants with knee osteoarthritis, aged from 35 to 82
Interventions	Classical acupuncture (CA) vs. Non-specific acupuncture (NA)
Outcomes	Knee Flexibility, WOMAC
	Knee flexibility improvement by 10 degree or more immediately was significant higher after classical acupuncture (75 of 116) compared to non-specific acupuncture (6 of 116)
	WOMAC success rates, defined as a WOMAC reduction by 50% were the largest immediately after classical acupuncture (85 of 116) as compared of non-specific acupuncture (56 of 116).
Others	Sources of funding not fully described

Table 4. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Max Karner et al 2012b
Methods	RCT Cross-over, Double blinded
Participants	116 participants with knee osteoarthritis, aged from 35 to 82
Interventions	Modern acupuncture (CA) vs. Non-specific acupuncture (NA)
Outcomes	Knee Flexibility, WOMAC
	Knee flexibility improvement by 10 degree or more immediately after modern acupuncture (41 of 116) compared to Non-specific acupuncture (6 of 116)
	WOMAC success rates, defined as a WOMAC reduction by 50%, after modern acupuncture (74 of 116) as compared of non-specific acupuncture (56 of 116).
Others	Sources of funding not fully described

Table 4. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Qi Wang et al 2020
Methods	A pilot randomized controlled trial, Single Blinded
Participants	30 participants with knee osteoarthritis, aged from 45 to 75
Interventions	Electronic acupuncture (EA) vs. Sham Electronic acupuncture (SA)
Outcomes	Proportion of responders, TUG, ROM, Lequesne index The proportion of responders in electroacupuncture group as week eight as twice as that in sham acupuncture group with no significantly difference. TUG (Time Up and Go Test): the proportion of responders achieving at least 1.14 seconds decrease in TUG at week eight compare with baseline. ROM: AROM and PROM were significant improvements from baseline to week eight in electroacupuncture group Lequesne index: there were significant improvements from baseline to week eight in electroacupuncture group
Others	The research was carried out at Beijing Hospital of Traditional Chinese Medicine.

Table 4. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Song Wei et al 2013a
Methods	Randomized controlled trail, Double-Blinded
Participants	79 participants with knee osteoarthritis, mean age: 70 years
Interventions	Meridian-Sinew Release Group vs. Control Group (conventional drug therapy)
Outcomes	VAS and WOMAC In meridian-sinew release group, change in the primary point of pain at week 12 was significantly greater than in control group.
Others	The participants were recruited from Guangzhou General Hospital of Guangzhou Military Command.

Data Component	Data Item
Literature Information	Song Wei et al 2013b
Methods	Randomized controlled trail, Double-Blinded
Participants	79 participants with knee osteoarthritis, mean age: 70 years
Interventions	Acupuncture Group vs. Control Group (conventional drug therapy)
Outcomes	VAS and WOMAC In acupuncture group, change in the primary point of pain at week 12 was significantly greater than in control group.
Others	The participants were recruited from Guangzhou General Hospital of Guangzhou Military Command

Table 4. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Zhang Lele et al 2019a
Methods	RTCs, Single-Blinded
Participants	90 participants with knee osteoarthritis, mean age: 55.2 + 6.0 years
Interventions	Acupuncture and Usual Care (AP+UC) vs. Usual Care (UC)
Outcomes	VAS and WOMAC
	VAS: The average pain VAS score in the AP+UC group decreased significantly by the end of 1st and 2nd week treatment as compared of UC group
	WOMAC: During the treatment from 1st to 2nd week, the pain scores of AP+UC was less than that of the UC group
Others	Sources of funding not fully described

Table 4. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Zhang Lele et al 2019b
Methods	RTCs, Single-Blinded
Participants	90 participants with knee osteoarthritis, mean age: 55.2 + 6.0 years
Interventions	Electroacupuncture and Usual Care (EA+UC) vs. Usual Care (UC)
Outcomes	VAS and WOMAC VAS: The average pain VAS score in the EA+UC group decreased significantly by the end of 1st and 2nd week treatment as compared of UC group WOMAC: During the treatment from 1st to 2nd week, the pain scores of EA+UC was less than that of the UC group
Others	Sources of funding not fully described

Table 4. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Pengli Jia et al 2016
Methods	Single-Blind, two arm, parallel, RTCs
Participants	28 participants with knee osteoarthritis, aged from 45 to 75
Interventions	Acupuncture at high sensitized points vs. Acupuncture at low/non- sensitized points
Outcomes	Retention rate, WOMAC, SF-12
	Retention rates were similar between the treatment groups, 14 (77.8%) patients in the high sensitization group completed the 16 week follow-up as compare to 14 (77.8%) patients in the low/non-sensitivity group.
	The WOMAC total score and WOMAC subscale s in the high-sensitization group were lower or very close to those in the control group at each assessment point.
	SF-12 physical health scores increased from baseline to week 12 then decreased slightly at week 16 in the high sensitivity group as compared of the low/non sensitivity group increase from baseline to week 4 then slightly decreased from week 8 to week 16.
	SF-12 mental health scores increased from baseline to week 4, then decreased from week 8 to week 12 in the high sensitization group, while continued to increase in the low/non-sensitization groups
Others	The participants were recruited from the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine in Sichuan province, China.

Table 4. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Yan Zhang et al 2016
Methods	Single-Blinded, RCTs
Participants	96 participants with knee osteoarthritis, age: 30 to 80 years
Interventions	Electro-acupuncture vs. Physiotherapy
Outcomes	WOMAC, and MRI scanning for T2 values WOMAC: In electroacupuncture group the total score of WOMAC and three subscales for pain, stiffness, and physical function on 4th weekend were significantly lower than those of the physical therapy group. MRI scanning for T2 values in anterior medial tibial sub-region (MTa) and anterior lateral tibial sub – region (LTa) were significant lower in electroacupuncture group on 4th weekend while no significance to T2 was detected in physical therapy group.
Others	The participants were recruited from the department of Orthopedic Surgery of Peking Union Medical College Hospital.

Table 4. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Tain-Qi Wang et al 2019
Methods	Double-Blinded, RTCs
Participants	58 participants with knee osteoarthritis rang age: 45 to 75 years
Interventions	Electro - acupuncture (EA) vs. Manual acupuncture (MA)
Outcomes	WOMAC, and VAS After 8 weeks of treatment, the response rate (define as a change of $\geq$ 50% from baseline in WOMAC total score) was 43% for electroacupuncture group and 30% for the manual acupuncture group VAS score at week 4, week 8, week 12, or week 16, there was no significant difference between electroacupuncture group and the manual acupuncture group.
Others	The participants were recruited from 3 hospitals: Beijing Hospital of Traditional Chinese Medicine, Beijing Friendship Hospital, and Beijing Jishuitan Hospital

Table 4. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Zheng-Tao Lv et al 2019a
Methods	Multicenter, three-arm parallel, RCTs, Single-Blinded
Participants	271 participants with knee osteoarthritis age range 50 years of older
Interventions	Strong Electroacupuncture vs. Sham Electroacupuncture
Outcomes	CMP, VAS, WOMAC, NPRS, ES, and PPI
	The mean of CMP function score was 9.49 at baseline and 24.34 at week 2 in the strong EA group as compared of 9.46 at baseline and 10.89 at week 2 in sham EA group.
	The CMP function score was observed increasing in the strong EA group than in the sham EA group
	VAS, WOMAC, NPRS, ES, and PPI were significantly lower in the strong EA group than in the sham EA group
Others	The participants were recruited from 5 hospitals in Wuhan, China.

Table 4. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Zheng-Tao Lv et al 2019b
Methods	Multicenter, three-arm parallel, RCTs, Single-Blinded
Participants	271 participants with knee osteoarthritis, age range 50 years of older
Interventions	Weak Electroacupuncture vs. Sham Electroacupuncture
Outcomes	CMP, VAS, WOMAC, NPRS, ES, and PPI
	The mean of CMP function score was 9.86 at baseline and 14.61 at week 2 in the weak EA group as compared of 9.46 at baseline and 10.89 at week 2 in sham EA group.
	The CMP function score was observed increasing in the weak EA group than in the sham EA group
	VAS, WOMAC, NPRS, ES, and PPI were significantly lower in the weak EA group than in the sham EA group
Others	The participants were recruited from 5 hospitals in Wuhan, China.

Table 4. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	LX Chen et al 2013
Methods	Double-Blinded, RCTS
Participants	213 participants with knee osteoarthritis, aged 40 years or older
Interventions	True Acupuncture + Exercise-based Physical Therapy (EPT) vs. Non-Penetrating Acupuncture + Exercise base Physical Therapy (EPT)
Outcomes	WOMAC, BPI Average pain, SF-36 Both treatment groups showed improvement from combined therapy with no difference between true acupuncture (31.6%) and non-penetrating acupuncture (30%) in WOMAC response rate. All secondary outcomes (BPI, SF-36) were also examined and showed no separation between the treatment groups.
Others	The participants were recruited from physical therapy departments at the Hospital of the University of Pennsylvania, Pennsylvania Hospital, and the Philadelphia VA Medical Center.

Table 4. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Yaun-Shi Liu et al 2013
Methods	RCTs, A multicenter
Participants	192 participants with knee osteoarthritis, aged from 40 to 65
Interventions	Long round needle therapy group (EG) vs. pharmacotherapy control Group (CG)
Outcomes	Therapeutic Effectiveness Index Therapeutic effectiveness at the end of treatment is significant difference, and the therapeutic effectiveness of EG is superior to the CG The therapeutic effectiveness at follow up 3 months is significant difference, and the therapeutic effectiveness of EG is superior to the CG.
Others	The participants were recruited from Institute of Acupuncture and Moxibustion, China Academy of Chinese Medicine Sciences; Guang'anmen Hospital, China Academy of Chinese Medicine Sciences; or Shandong Laizhou Maternity and Child Care Hospital.

3. Assessment of Risk of Bias (RoB)

I evaluated the risk of bias in the ten clinical trial literature selected for systematic review. Using software provided by RevMan 5.4 for the types of risk of bias evaluated according to the criteria. The graph of the comprehensive qualitative evaluation is shown in Figure 4.

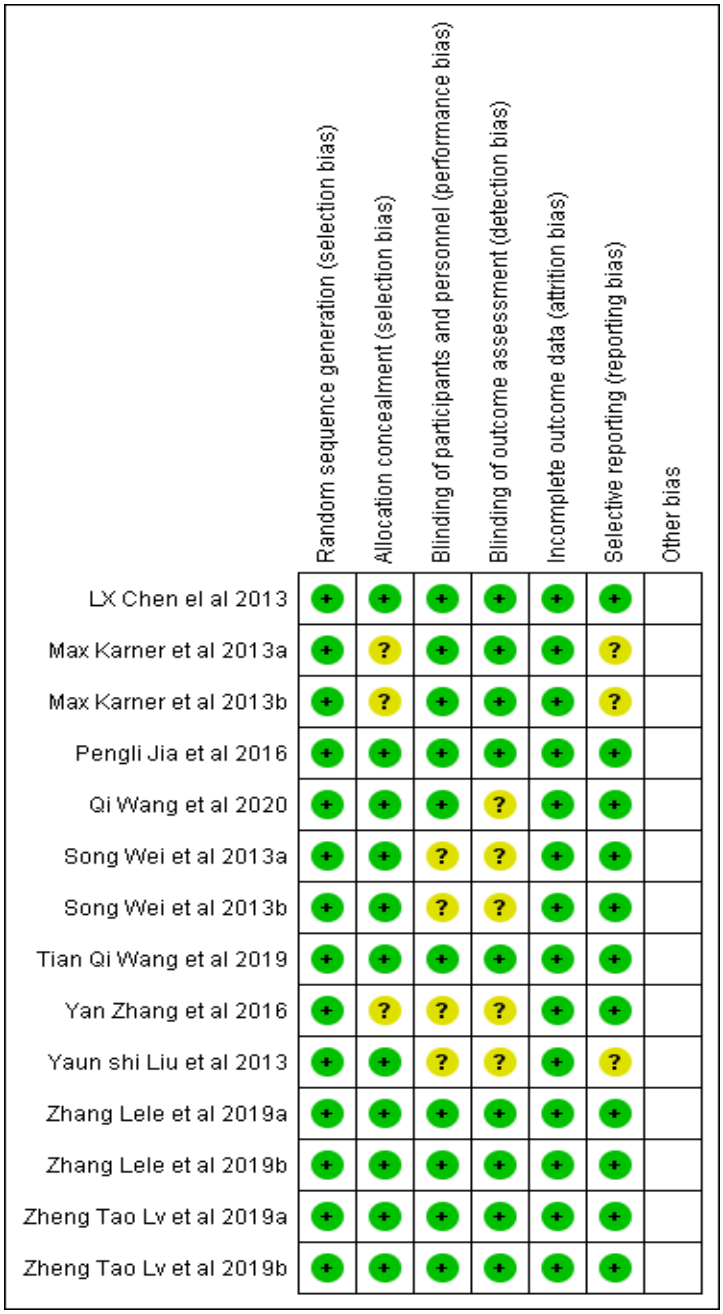

Figure 4. Risk of bias summary.

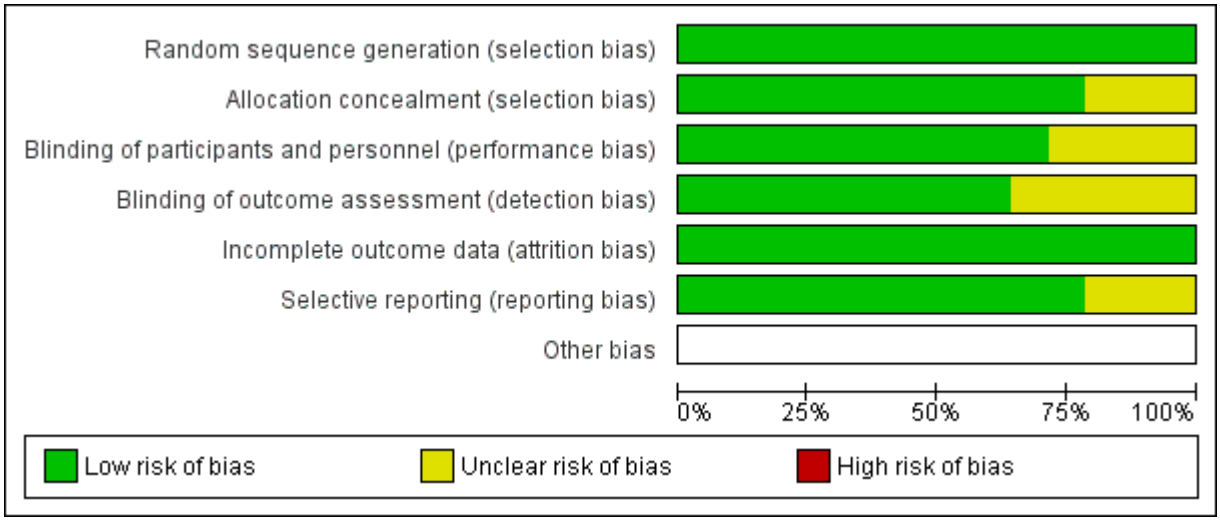

Figure 5. Risk of bias distribution graph.

In the allocation concealment 3 out of 14 cases (21.42%) unclear risk because of one not mention about allocation (Yan Zhang et al, 2016), another two using three differently coloured pens at random choice (Max Karner et al 2013a, 2013b).

In the blinding of participants and personnel 4 out of 14 cases (28.57%) unclear risk because there were not mention about blinding of participant and personnel (Song Wei et al, 2013a, 2013b; Yuan Zhang el al, 2016; and Yuan Shi Liu et al 2013).

In the blinding of outcome assessment 5 out of 14 cases (35.71%) unclear risk because there are four cases were not mention about blinding of outcome assessment (Song Wei et al, 2013a, 2013b; Yuan Zhang el al, 2016; and Yuan Shi Liu et al 2013). Another one case stated that blinding of the acupuncturist was not carried out because of the nature of the intervention (Qi Wang et al, 2020)

In the selective reporting 3 out of 14 cases (21.42%) unclear risk because of one reported outcome measures only therapeutic effectiveness index (Yuan Shi Liu et al, 2013).

Another two reported outcome measures only knee flexity and WOMAC (Max Karner et al 2013a, 2013b) (Figure 5).

4. Heterogeneity analysis

In the outcomes of LX Chen 2013, Max Karner 2013, and Pengli Jia 2016, etc.

To examine whether the confidence intervals and the directionality of the treatment effect values overlap, Heterogeneity test, the Chi^2 statistics and Higgins's I^2 was used. The result is shown in Table 5. The heterogeneity test was performed in 5 individual result items including VAS pain level, WOMAC score, WOMAC success rate, CMP function, and Knee ROM and the remaining items were excluded from the analysis.

As shown in Table 5, Knee ROM in the item I^2 value was 0%, indicating no significant heterogeneity. In WOMAC success rate, I^2 was 65% indicating substantially heterogeneity.
In the item of VAS pain level, WOMAC score, and CMP function, I^2 value were 94%, 99%, and 100% respectively, indicating significant heterogeneity.

On the other hand, the p-value in Chi^2 statistics was statistically significant at (p-value < 0.05) in all 4 items, except, Knee ROM not significant (p-value = 0.65)
As above, the fixed effect models were analyzed.

Table 5. Heterogeneity of Outcomes from LX Chen 2013, Max Karner 2013, Pengli Jia 2016, etc.

Outcome	Q	df	p-value	I^2
VAS Pain Level	77.76	5	<0.00001	94
WOMAC Score	635.29	9	<0.00001	99%
WOMAC Success Rate	8.66	3	0.03	65%
CMP Function	257.68	1	<0.00001	100%
Knee ROM	0.20	1	0.65	0%

5. Meta-analysis

Using the RevMan 5.4, the outcome of fourteen subgroups in the ten trails, were meta-analysis and show as a forest plot for VAS, WOMAC score, WOMAC success rate, CMP function, TUG, Knee ROM, Lequesne index score (Figure 6 to 12).

The visual analog scale (VAS) for pain is a straight line with one end meaning no pain and the other end meaning the worst pain imaginable. A patient marks a point on the line that matches the amount of pain he or she feels. It may be used to help choose the right dose of pain medicine (Appendix 2).

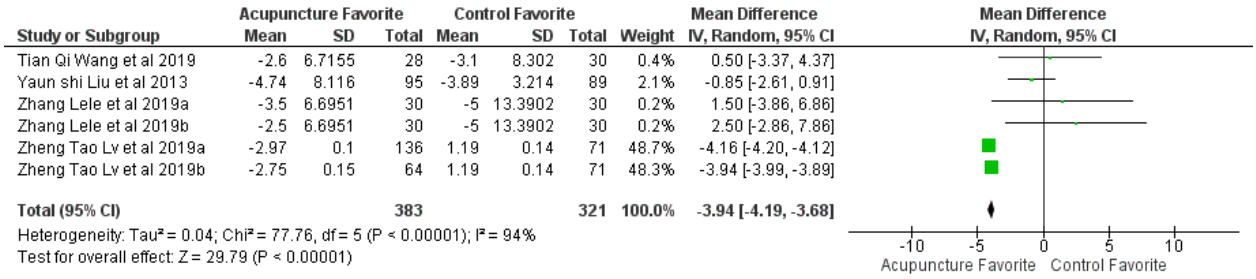

Figure 6. Effect of acupuncture therapy on the VAS pain score, Forest plot.

The six subgroups in four trails (Tian Qi Wang 2019, Yuan shi Liu 2013, Zhang Lele 2019, and Zheng Tao Lv 2019) involving 704 patients were included in the meta-analysis. The results indicated that the improvement in the total effectiveness rate among the different control groups the VAS pain score were significant lower in the acupuncture groups than in the control groups [MD -3.49 (-4.19, -3.68), 95% CI, p<0.00001) The level of heterogeneity (I^2) in VAS score was 94% (Figure 6).

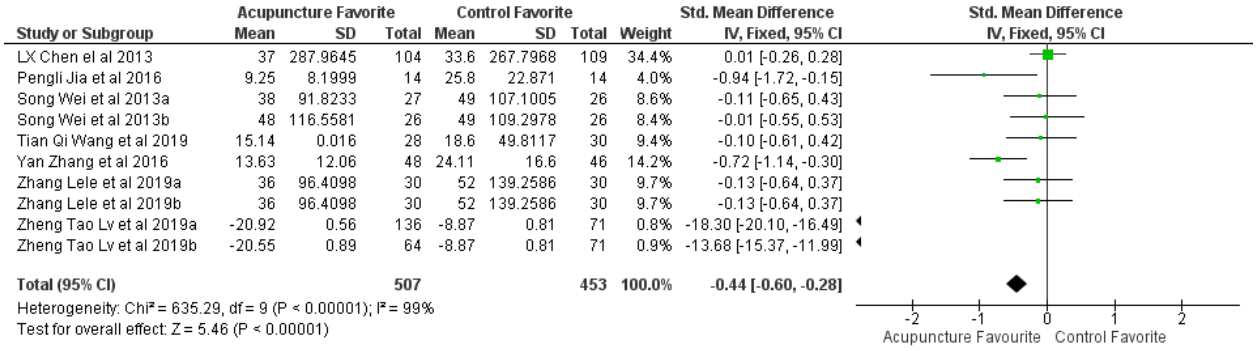

Figure 7. Effect of acupuncture therapy on the WOMAC score, Forest plot.

The WOMAC is a widely used self-administered health status measure used in assessing pain, stiffness, and function in patients with OA of hip or knee. It is also has been used to assess back pain, rheumatoid arthritis, juvenile rheumatoid arthritis, SLE, and fibromyalgia (Appendix 3).

The 10 subgroups in six trails involving 960 patients were included in the meta-analysis. The results indicated that the WOMAC score were significant lower in the acupuncture groups than in the control groups [MD -0.44 (-0.60, -0.28), 95% CI, p<0.00001). The level of heterogeneity (I^2) in WOMAC score was 99%. However, there was one study, LX Chen 2013, showed WOMAC score no significant difference between acupuncture group and control group (Figure 7).

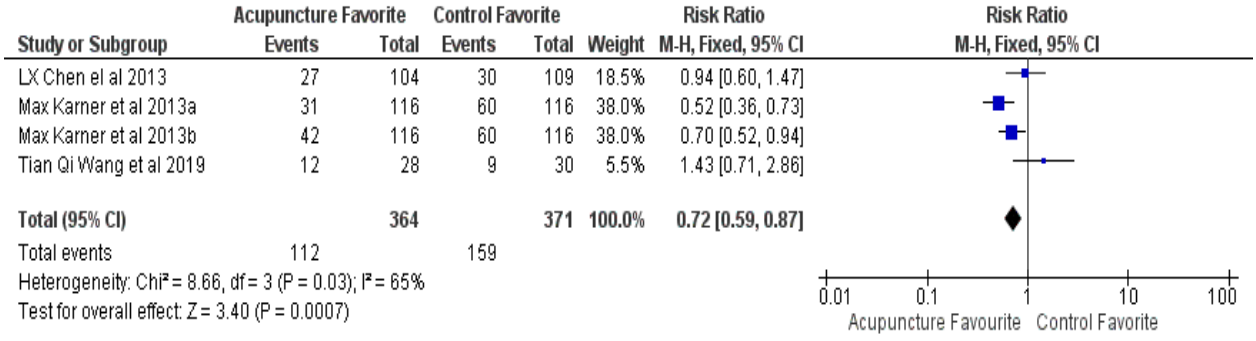

Figure 8. Effect of acupuncture therapy on the WOMAC success rate score, Forest plot.

The four subgroups in three trails (Lx Chen 2013, Max Karner 2013, and Tian Qi Wang 2019) involving 735 patients were included in the meta-analysis. The results indicated that the total WOMAC success rate were significant in the acupuncture groups than in the control groups [RR 0.72 (0.59, 0.87), 95% CI, p = 0.03]. The level of heterogeneity (I^2) in WOMAC success rate score was 65%. Although significant difference was observed, there were two studied LX Chen 2013 and Tian Qi Wang 2019 did not reach statistical significant (Figure 8).

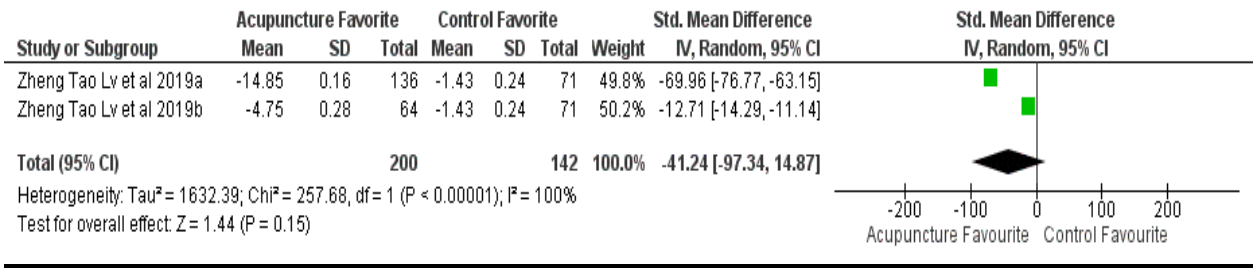

Figure 9. Effect of acupuncture therapy on the CPM function, Forest plot.

Conditioned Pain Modulation (CMP) is a term to describe one of the psychophysical paradigms in which central pain inhibition is tested by means of "pain inhibits pain" (Medoc, 2020). CMP is impaired in people with chronic pain such as knee osteoarthritis.

The 2 subgroups in one trail (Zhang Tao Lv, 201) involving 342 patients were included in the meta-analysis. The results indicated that the total CMP function were improved significant in the acupuncture groups than in the control groups [SD -41.24 (-97.34, 14.87), 95% CI, $p < 0.00001$]. The level of heterogeneity (I^2) in CMP function was 100% (Figure 9).

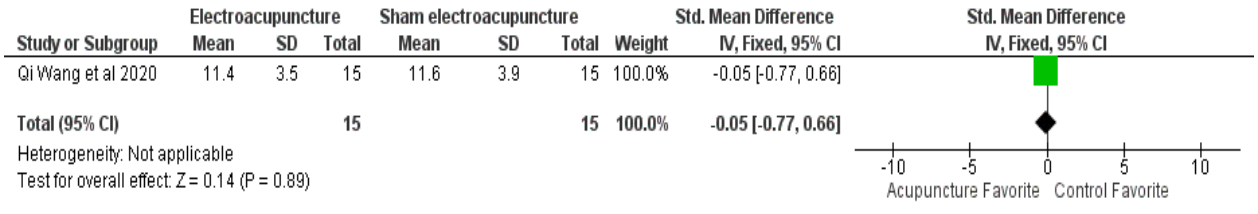

Figure 10. Effect of acupuncture therapy on the Time Up & Go (TUG), Forest plot.

The TUG is a general physical performance test used to assess mobility, balance and locomotors performance in elderly people with balance disturbances. More specifically, it assesses the ability to perform sequential motor tasks relative to walking and turning (Stroke Engine, 2021) (Appendix 4).

In Qi Wang 2020, involving 30 patients were included in the meta-analysis. The results indicated that there was no statistic significant difference in TUG between the electroacupuncture group and the control group [SD -0.05 (-0.77, -0.66), 95% CI, p=0.89]. The level of heterogeneity (I^2) in TUG was not applicable (Figure 10).

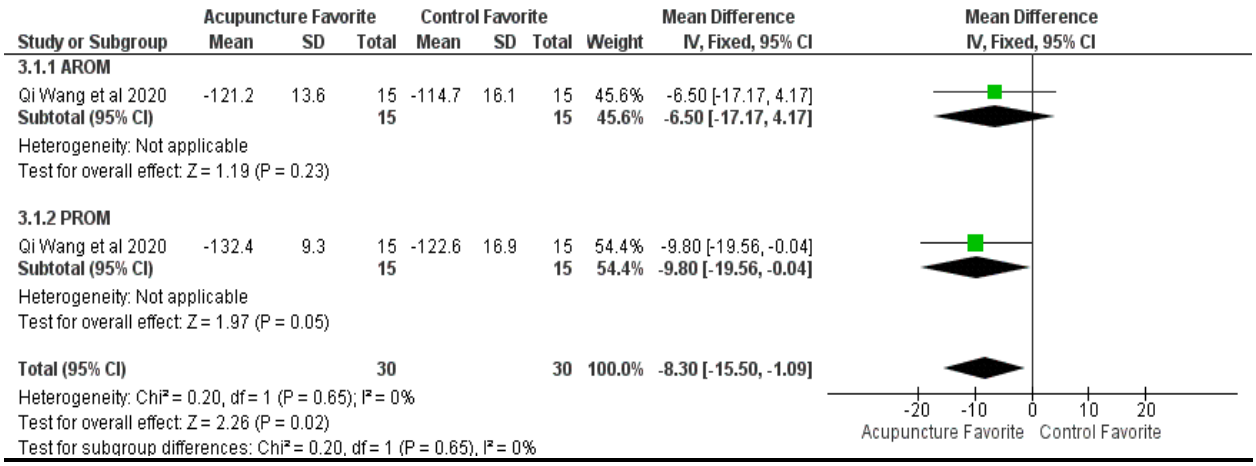

Figure 11. Effect of acupuncture therapy on the Knee ROM, Forest plot.

In Qi Wang 2020, involving 30 patients were included in the meta-analysis. The results indicated that the knee ROM, both AROM and PROM were statistically significant improvements in the electroacupuncture groups than the control groups [MD -8.30 (-15.50, -1.09), 95% CI, p=0.0.65]. The level of heterogeneity (I^2) in knee ROM was 0% (Figure 11).

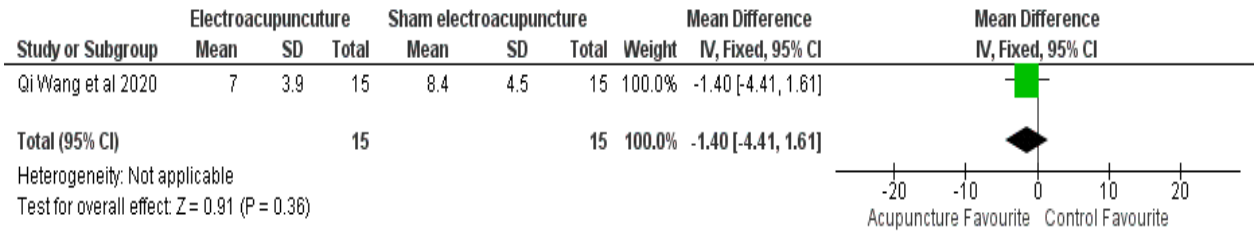

Figure 12. Effect of acupuncture therapy on the Lequesne Index score, Forest plot.

Lequesne index is used to evaluate severity and activity of KOA. It is includes 11 questions regarding pain, walking ability, and daily activity. The score range from 0 to 24 points. Higher score indicate worse physical function (Appendix 5).

In Qi Wang 2020, involving 30 patients were included in the meta-analysis. The results indicated that the Lequesne Index was statistically significant in the electroacupuncture groups than the control groups [MD -1.40 (-4.41, 1.61), 95% CI, p=0.36]. The level of heterogeneity (I^2) in Lequesne Index score was not applicable (Figure 12).

6. Identification of Reporting Bias

In order to check for reporting bias such as WOMAC Score, WOMAC Success Rate, VAS pain score, Knee ROM, Lequesne Index Score, Timed Up and Go (TUG) by performing a funnel plot of 6 result items Overestimation of the summary estimate of treatment effect was prevented. All 6 result items although it appeared symmetrically around the baseline, but the number of synthesized documents was less than 10, therefore the results were not significant (Figure 13 to 18).

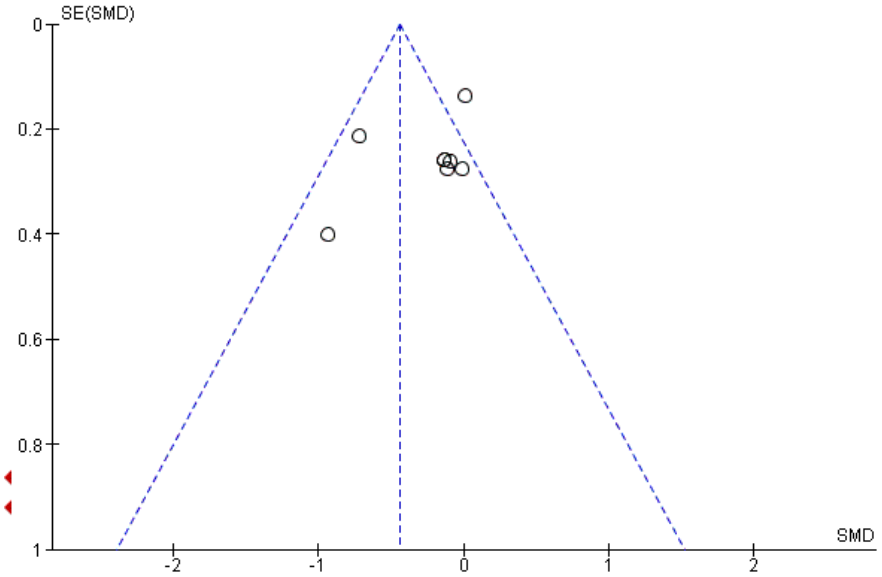

Figure 13. Funnel Plot Comparison of WOMAC Score

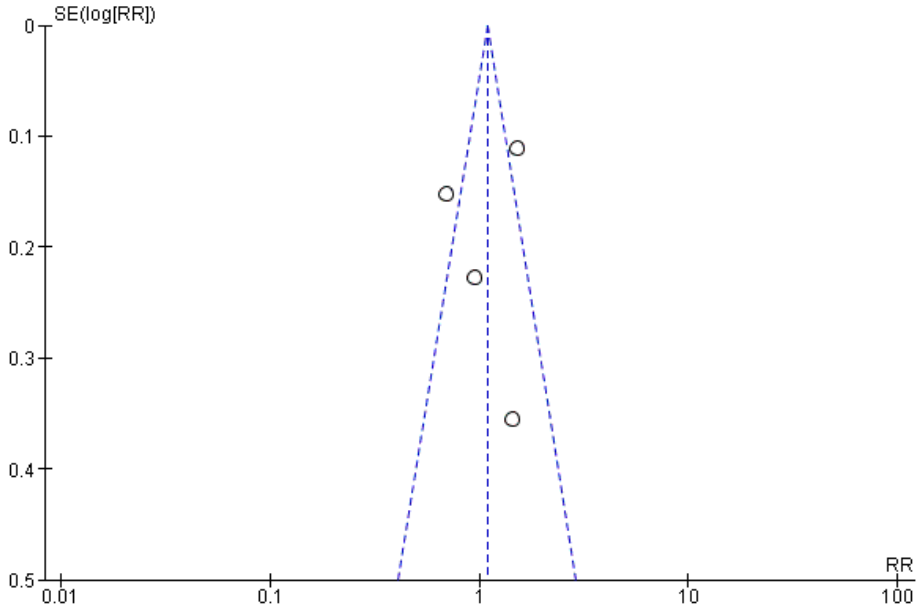

Figure 14. Funnel Plot Comparison of WOMAC Success Rate

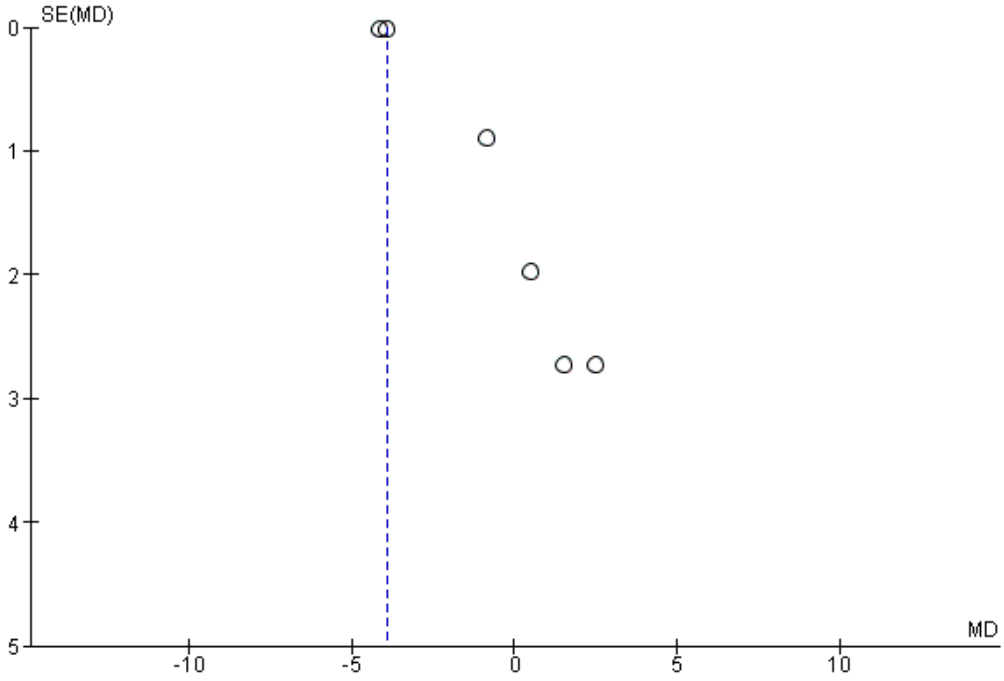

Figure 15. Funnel Plot Comparison of VAS pain score

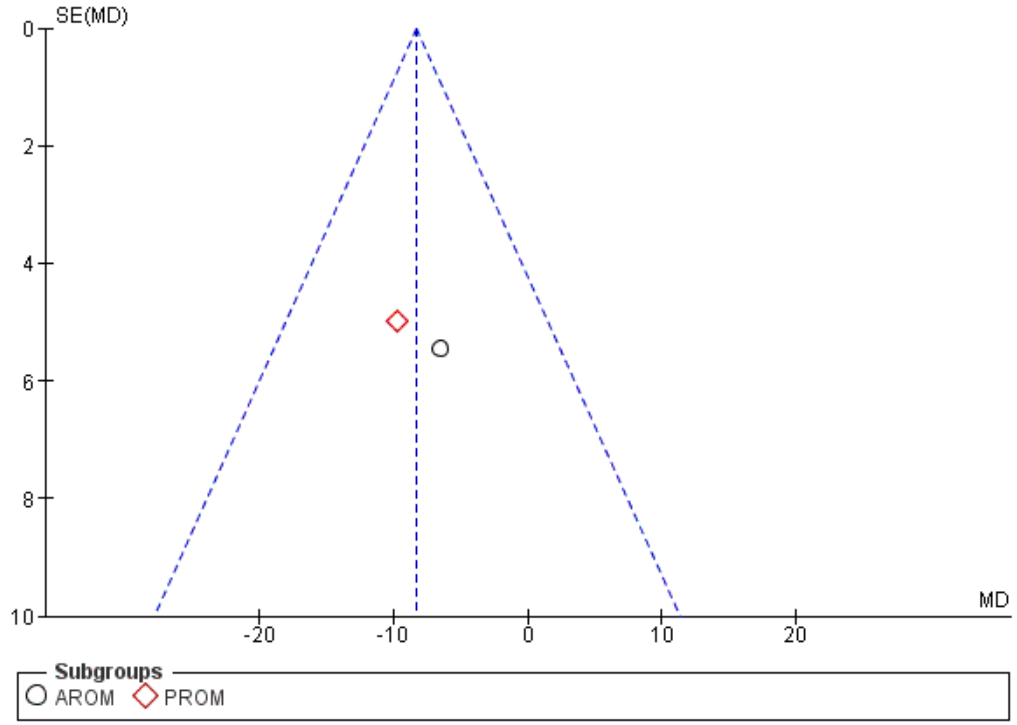

Figure 16. Funnel Plot Comparison of Knee ROM

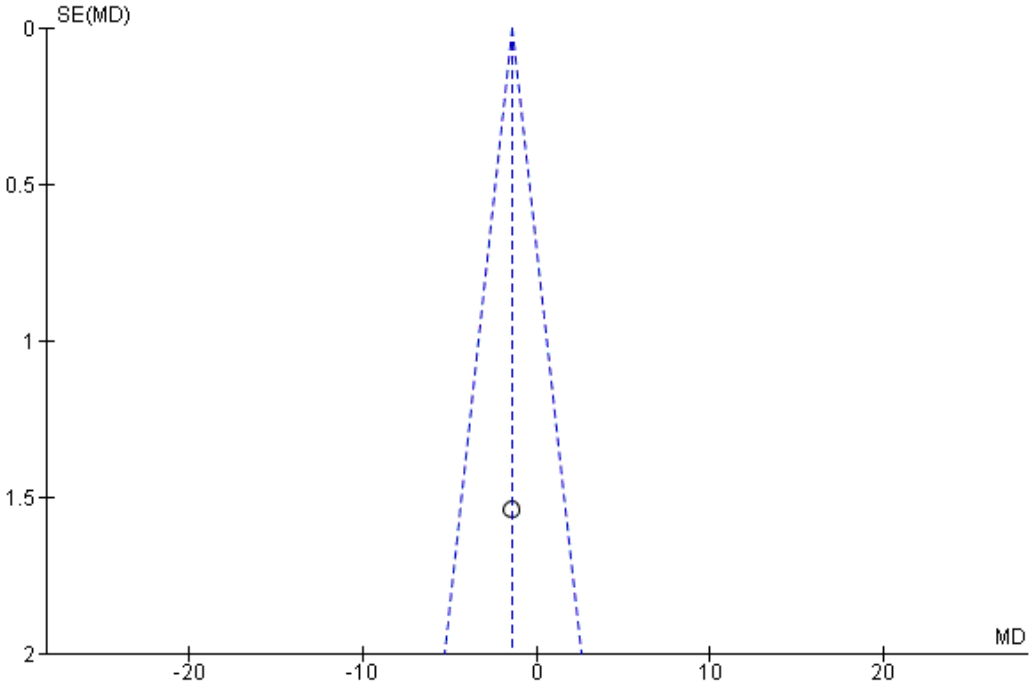

Figure 17. Funnel Plot Comparison of Lequesne Index Score

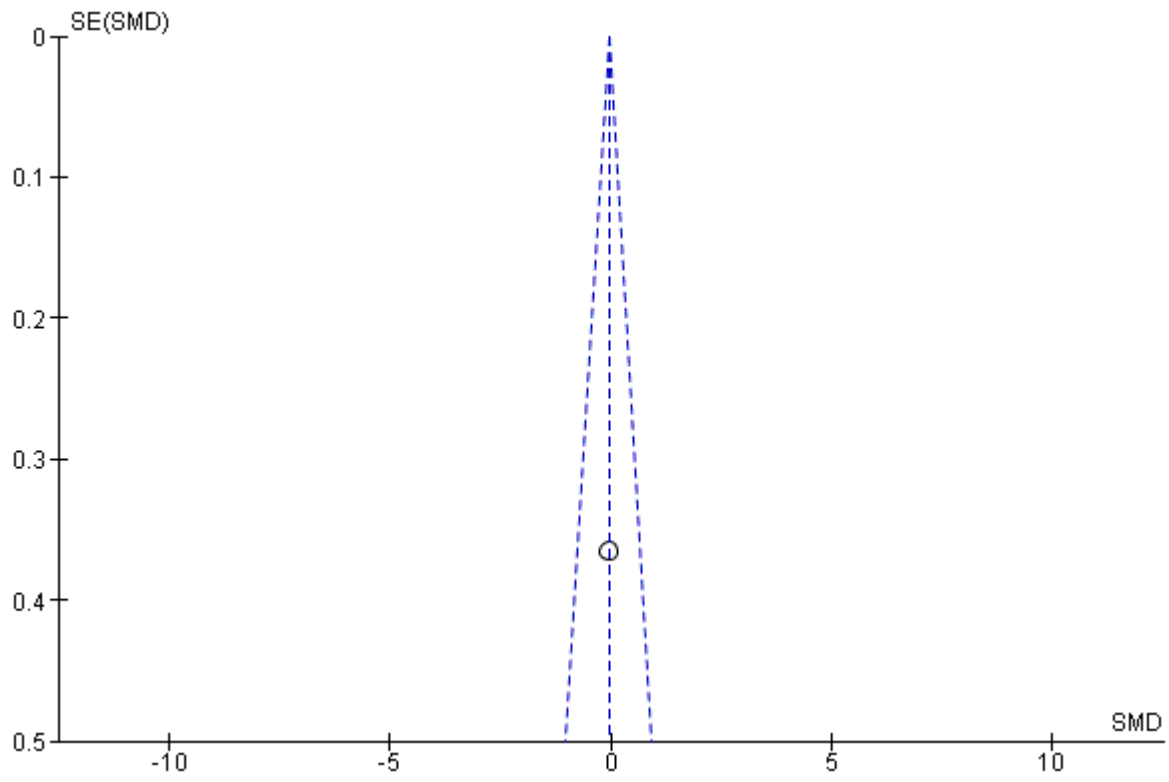

Figure 18. Funnel Plot Comparison of Time Up & Go (TUG)

7. Confirmation of safety and side effects

Table 6 describes safety and side effects from 10 clinical papers.

Based on this, there are no concerns about the safety and side effects of Acupuncture intervention for the patient who has knee osteoarthritis.

Table 6: Descriptions on the Safety and/or Adverse Effect of Acupuncture Intervention to KOA participants

Study	Quote
LX Chen 2013	A few reported minor adverse effect such as pain, muscle soreness, and swelling.
Max Karner 2013	No specific description.
Pengli Jia 2016	No adverse events occurred.
Qi Wang 2020	Adverse effect was not reported in this study.
Song Wei 2013	No adverse events occurred during the trial.
Tian Qi Wang 2019	Rate of adverse events were low and similarly distributed between groups. Both EA and MA interventions in KOA were feasible and appeared safe.
Yan Zhang 2016	Both acupuncture and physiotherapy were tolerated in this studied and all the participants completed the trail.
Yuan Shi Liu 2013	No specific description.
Zhang Lele 2019	No specific description
Zheng Tao Lv 2019	Adverse events were recorded such as bleeding, subcutaneous hemorrhage, and pain

IV. DISCUSSION

The systemic review and meta-analysis of 10 randomized control trials, including 1,199 participants indicated that the intervention group who received acupuncture and/or electro-acupuncture therapy has larger beneficial effects than the control group who received sham acupuncture, physical therapy, and/or conventional drug therapy. In addition, many studies have shown that acupuncture and electroacupuncture are benefit for knee osteoarthritis in alleviating pain and improving physical function. Overall, acupuncture/electroacupuncture therapy appears to be safe method for reducing pain in patients with knee osteoarthritis.

The meta-analysis outcome measures for this review including VAS, WOMAC, WOMAC success, rate, CMP function, TUG, Knee ROM, and Lequesne Index. The finding is supported by the existing evidence. There are 4 RCTs concluded that the VAS pain score were significant lower in the acupuncture groups than in the control group. In 1 of 4 RCTs, Song Wei 2013, indicated that change in primary point of pain at week 12 was significantly greater in meridian sinew release group and acupuncture group than in conventional drug therapy group. In Zhang Lele 2019, indicated that the average pain VAS score in acupuncture group decreased significantly by the end of 1st and 2nd week of treatment as compare of unusual care.

There are 6 RCTs indicated that the WOMAC score were significant lower in the acupuncture intervention groups than in the control groups. One of the studied, Yaun Zhang 2016, indicated that in electroacupuncture the total score of WOMAC and three subscales for pain, stiffness, and physical function on 4th week were significantly lower than those of the physical therapy. However, there was one study, LX Chen 2013, indicated WOMAC score no

significant difference between true acupuncture and exercise-base physical therapy as compare of non-penetrating acupuncture and exercise-base physical therapy.

There are 3 RCTs indicated that the WOMAC success rate were significant in the acupuncture groups than in the control groups. In Max Karner 2012, also stated that the total WOMAC success rate defined as WOMAC reduction by 50% were the largest immediately after classical acupuncture as compared of non-specific acupuncture. The CMP function was conducted in one trails Zheng Tao Lv 2019, indicated that total CMP function were improved significantly in strong electroacupuncture group than in the sham electroacupuncture group.

The only trail, Qi Wang 2020, indicated that there was no significant difference in TUG between electroacupuncture group and control group. There were significant improvements Knee ROM and Lequesne Index from baseline to week eight in electroacupuncture group. However, there was too little information in one RCTs. The simple size was too small to provide powerful evidence. Therefore, evidence on the effectiveness of acupuncture in improving knee ROM and Lequesne Index of patient with knee OA was not powerful enough.

Acupuncture points for KOA that used in the 10 RCTs were the standard points included: 1) Primary points: ST34, ST35, SP9, SP10, GB34, Xi Yan. 2) Secondary points: selected 2 or 3 points from ST32, ST34, ST36, ST40, KD10, KD3, LV3, LV7, LV8, UB39, UB40, UB57, UB60, GB31, GB36, GB41, SP4, SP5, SP6, He Ding, and Ashi points.

The results of meta-analysis were meaningful for clinical practice, and indicate that acupuncture may be better than drugs, or usual care in terms of reducing the pain and improving the physical function of knee OA patients. However, there are some limited of this systemic review, due to the overall methodological quality of the RCTs was moderate. Many of the

included RCTs had unclear risk bias. One study was not mention about allocation; four studies were not mention about blinding of participant and personnel; five studies were not mention about blinding of outcome assessment. Another one study stated that blinding of the acupuncturist was not carried out because of the nature of the intervention.

V. CONCLUSION:

In conclusion, the results of the meta-analysis in this study reported that VAS pain score [MD -3.94], WOMAC score [SMD -0.44], WOMAC success rate score [RR 0.72], and CPM function [SMD -41.24] showed significant improvement, however, Time Up & Go (TUG) [SMD -0.05] did not show significance. This study indicated that acupuncture therapy may be effective in alleviating pain and enhancing physiological function of patients with knee osteoarthritis. Acupuncture might be also more effective than usual drug therapy in improving the daily of living of patients with knee osteoarthritis. In addition, acupuncture therapy appears to be safe method for reducing pain in patients with knee osteoarthritis. Acupuncture may have a strong impact on pain and physiological function. Therefore, acupuncture is a feasible alternative for knee osteoarthritis. In future research requires confirmation by larger, adequately power, randomized controlled trials.

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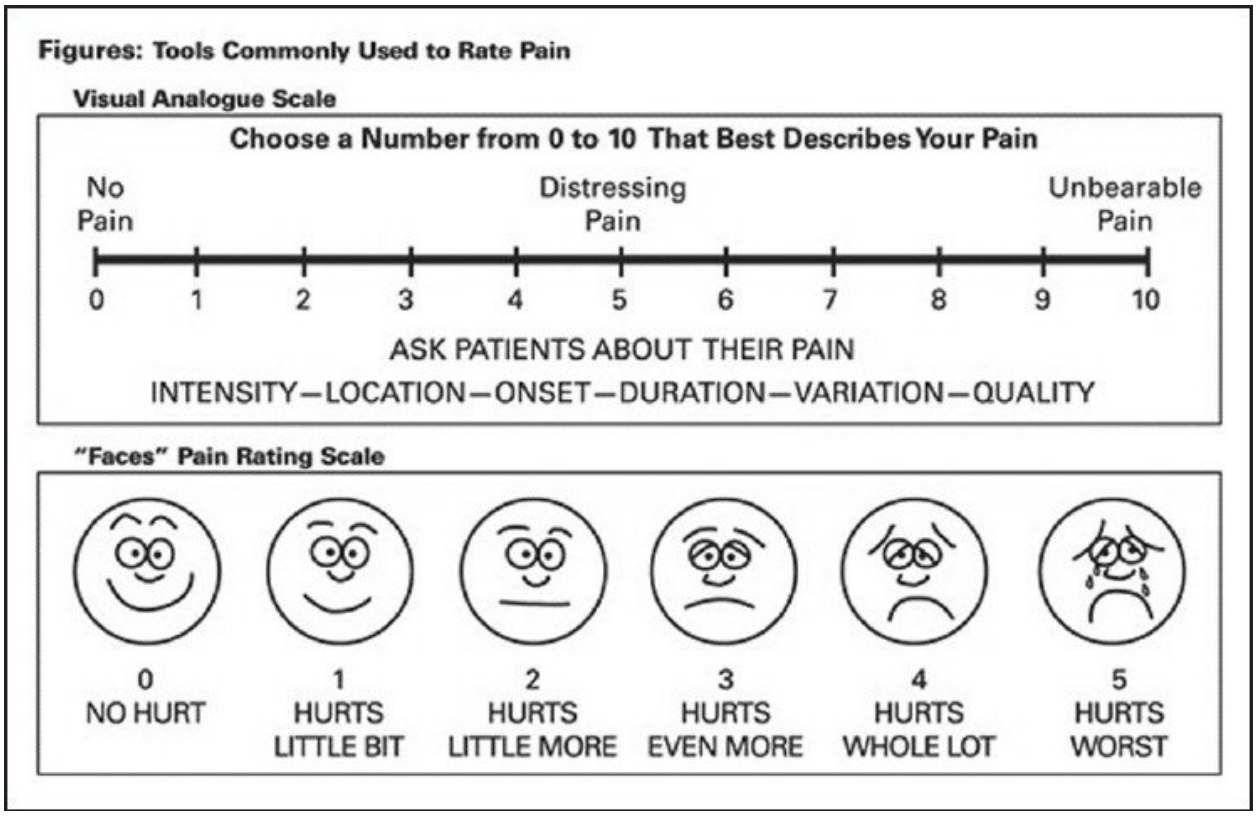
APPENDIX

Appendix 1: Visual Analogue Scale (VAS)



Appendix 2: Western Ontario and McMaster University Osteoarthritis Index (WOMAC)

Name: _____ Date: _____

Instructions: Please rate the activities in each category according to the following scale of difficulty: 0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely

Circle **one number** for each activity

Pain	1. Walking	0	1	2	3	4
	2. Stair Climbing	0	1	2	3	4
	3. Nocturnal	0	1	2	3	4
	4. Rest	0	1	2	3	4
	5. Weight bearing	0	1	2	3	4
Stiffness	1. Morning stiffness	0	1	2	3	4
	2. Stiffness occurring later in the day	0	1	2	3	4
Physical Function	1. Descending stairs	0	1	2	3	4
	2. Ascending stairs	0	1	2	3	4
	3. Rising from sitting	0	1	2	3	4
	4. Standing	0	1	2	3	4
	5. Bending to floor	0	1	2	3	4
	6. Walking on flat surface	0	1	2	3	4
	7. Getting in / out of car	0	1	2	3	4
	8. Going shopping	0	1	2	3	4
	9. Putting on socks	0	1	2	3	4
	10. Lying in bed	0	1	2	3	4
	11. Taking off socks	0	1	2	3	4
	12. Rising from bed	0	1	2	3	4
	13. Getting in/out of bath	0	1	2	3	4
	14. Sitting	0	1	2	3	4
	15. Getting on/off toilet	0	1	2	3	4
	16. Heavy domestic duties	0	1	2	3	4
	17. Light domestic duties	0	1	2	3	4

Total Score: _____ / 96 = _____%

Comments / Interpretation (to be completed by therapist only):

Appendix 3: Time Up and Go (TUG)

ASSESSMENT

Timed Up & Go (TUG)

Patient _____

Date _____

Time ☐ AM ☐ PM

Purpose: To assess mobility

Equipment: A stopwatch

Directions: Patients wear their regular footwear and can use a walking aid, if needed. Begin by having the patient sit back in a standard arm chair and identify a line 3 meters, or 10 feet away, on the floor.

NOTE: Always stay by the patient for safety.

① **Instruct the patient:**

When I say "Go," I want you to:

1. Stand up from the chair.
2. Walk to the line on the floor at your normal pace.
3. Turn.
4. Walk back to the chair at your normal pace.
5. Sit down again.

② **On the word "Go," begin timing.**

③ **Stop timing after patient sits back down.**

④ **Record time.**

Time in Seconds: _____

An older adult who takes ≥12 seconds to complete the TUG is at risk for falling.

OBSERVATIONS

Observe the patient's postural stability, gait, stride length, and sway.

Check all that apply:

- ☐ Slow tentative pace
- ☐ Loss of balance
- ☐ Short strides
- ☐ Little or no arm swing
- ☐ Steadying self on walls
- ☐ Shuffling
- ☐ En bloc turning
- ☐ Not using assistive device properly

These changes may signify neurological problems that require further evaluation.

CDC's STEADI tools and resources can help you screen, assess, and intervene to reduce your patient's fall risk. For more information, visit www.cdc.gov/steadi

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

2017

STEADI Stopping Elderly Accidents, Deaths & Injuries

Appendix 4: Lequesne Index

Index of Severity for Osteoarthritis of the Knee by Lequesne et al

Overview:

Lequesne et al developed an index of severity for osteoarthritis for the knee (ISK). This can be used to assess the effectiveness of therapeutic interventions.

Sections for index:

(1) pain or discomfort

(2) maximum distance walked

(3) activities of daily living

I Pain or Discomfort

Parameter	Finding	Points
pain or discomfort during nocturnal bedrest	none	0
	only on movement or in certain positions	1
	without movement	2
duration of morning stiffness or pain after getting up	none	0
	< 15 minutes	1
	>= 15 minutes	2
remaining standing for 30 minutes increases pain	no	0
	yes	1
pain on walking	none	0
	only after walking some distance	1
	early after starting	2
pain or discomfort after getting up from sitting without use of arms	no	0
	yes	1

where:

- A change in a 1991 version was to have the duration of morning stiffness scored 0 if it was 1 minute or less and 1 if it was from 1 to less than 15 minutes.

- Pain on walking in a 1991 version expanded "early after starting" to "after initial ambulation and increasingly with continued ambulation"

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pain or discomfort after getting up from sitting without use of arms	no	0
	yes	1

where:

- A change in a 1991 version was to have the duration of morning stiffness scored 0 if it was 1 minute or less and 1 if it was from 1 to less than 15 minutes.

- Pain on walking in a 1991 version expanded "early after starting" to "after initial ambulation and increasingly with continued ambulation"

	with mild difficulty	0.5
	with moderate difficulty	1.0
	with marked difficulty	1.5
	impossible	2.0

index of severity =

= SUM(points for all parameters)

Interpretation:

• minimum points for each section: 0

• maximum points for each section: 8

• minimum index score: 0

• maximum index score: 24

Index Score	Handicap
0	none
1 - 4	mild
5 - 7	moderate
8 - 10	severe
11 - 13	very severe
>= 14	extremely severe

Modifications

The index was modified in 1997 with some minor changes to morning stiffnes and termed the "algofunctional index".

References:

Lequesne M Mery C et al. Indexes of severity for osteoarthritis of the hip and knee. Scand J Rheumatology. 1987; Supplement 65: 85-89.

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