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Review Article

Efficacy of acupuncture in pain management of chronic diseases of bone and joint: a review of literature

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Abstract: Acupuncture is in use in China for several millennia as a procedure believed to restore altered energy balance of the body due to any disease through insertion of needles at specific points called energy channels. The use of acupuncture in various types of musculoskeletal pain is on the rise. The analgesic action of acupuncture is mediated by local production of endogenous opioid peptides (EOP) and modulation of nociceptor function. Several high quality randomized clinical trials (RCT) have generally concluded that acupuncture is effective in relieving back pain compared with no treatment and comparable to usual care for back pain. Several high quality studies found significant pain reduction in patients with osteoarthritis of knee although lack of analgesic effect of acupuncture in this disease setting has also been reported. High quality studies on the effect of acupuncture in rheumatoid arthritis (RA) are lacking. When two well-designed (double-blind, randomized and placebo-controlled) studies with RA patients were considered, one found significantly improved tender joint and pain by traditional acupuncture but the other failed to find any effect of acupuncture over placebo. In case of gouty arthritis, a systematic meta-analysis found significant efficacy of acupuncture treatment in decreasing blood uric acid and improving the overall quality of life. Effect of acupuncture on post-menopausal osteoporosis remains understudied. Results from preclinical studies in gonadectomised rats suggests bone conserving effect of acupuncture; however, efficacy trials in post-menopausal osteoporotic patients are not yet available. The goal of the review was to comprehensively discuss the scientific basis of acupuncture in alleviating chronic pain arising from bone and joint diseases.

Keywords: Acupuncture, osteoarthritis, rheumatoid arthritis, osteoporosis, pain, anti-inflammatory agents

Introduction

Together, osteoporosis and arthritis are the biggest contributors of pain associated with all bone and joint pathologies. Osteoporosis is a metabolic bone disease having several aetiology, most common being the deficiency of gonadal steroids (estrogen and androgen), ageing, iatrogenic, hyperparathyroidism and renal failure. Osteoporosis increases the risk of fragility fractures which are very difficult to heal. Arthritis is broadly classified into rheumatoid arthritis (RA) and osteoarthritis (OA). RA is a chronic and progressive inflammatory disease, characterized by synovial inflammation giving rise to destruction of joint tissue [1]. OA is a degenerative disease of joints, characterized by gradual loss of cartilage and subchondral bone [2].

Osteoporosis therapies are classified into a) anti-resorptives (to inhibit bone loss) and b) osteoanabolic (to stimulate bone formation). Most commonly used anti-resorptive therapies are various bisphosphonates, raloxifene (selective estrogen receptor modulators) and neutralization of receptor activator of nuclear factor kappaB ligand (RANKL). Recombinant human parathyroid hormone (1-34) is the only osteoanabolic therapy [3, 4]. Because, inflammatory-induced bone loss as observed in RA is mediated by RANKL and tumor necrosis factor (TNF), antibody based neutralization of RANKL (denosumab) and TNFα (infliximab) are clinically used therapies of RA. Although, there are therapies for osteoporosis and RA, the treatments are long term and diseases are not cured. Bone loss and joint destruction would resume if treatments for osteoporosis and RA are stopped.

Also, there are various adverse effects of these treatments which precludes treatment adherence by patients. Given this state of clinically used therapies, many patients have turned to alternative medicine for osteoporosis and RA [5]. For OA, there is presently no disease modifying therapy approved by the U.S. Federal Drug Administration (FDA).

For arthritis and osteoporosis, pain is the most debilitating aspect and chronic use of analgesics poses serious adverse outcomes. Because acupuncture is used as a sensory stimulation therapy for nearly 3 millennia, many patients of osteoporosis and arthritis seek this therapy. Because bone and joint pains are chronic in nature and individual patient data meta-analyses demonstrate that significantly less pain been experienced by patients administered acupuncture in variety of conditions with chronic pain [6], acupuncture appears to be a referral option for pains associated with bone and joint diseases. This review discussed the analgesic effect of acupuncture in various musculoskeletal diseases.

Description of acupuncture

In traditional Chinese medicinal (TCM) practice, hair-thin metal needles are inserted in specific points such as along the meridians or at the tender points, so called acupuncture points to relieve pain and promote wellbeing [7]. These are called *"Ashi"* points in Chinese medicine. Needles are inserted up to depths that would cause a sensation that combines tingling, soreness, distension and heaviness to the patient and is termed as "*De qi*" [8]. Also, TCM practitioner could perceive the needle being "grabbed" by the tissue, which enables her/him to assess correct insertion. Heat and electric stimulation may be applied to promote needle sensation. Following insertion, patient has to remain still for about 20-40 minutes and during this needle retention period, the TCM practitioner frequently examines tongue and feels pulse. Safety of acupuncture has been established in large prospective studies and the most common side effects are hematoma, bruise, needling pain and dizziness [9]. Most patients find acupuncture to be calming and relaxing. However, in some rare cases headache, severe fatigue and pneumothorax has been reported for needling in the chest area [10].

Electroacupuncture is a modified version of conventional acupuncture wherein electrical stimulation is applied using acupuncture needles. Because body tissue could be viewed as an electrical conductor of ions and electrical impulses could not only strengthen the acupoint stimulation applied through the needles but also accomplish better elimination of polarization of cell membrane. Changes brought about by electroacupuncture in the distribution and concentration of the ions in the tissues could underlie more effective pain mitigation by electroacupuncture over conventional acupuncture [11]. Low frequency electroacupuncture stimuli ranging from 1-5 Hz promote secretion of analgesic neurotransmitters and have sedative effects on the pain conduction pathway [12].

Mechanism of action of acupuncture

A research group of acupuncture anesthesia in Peking University, China undertook the challenge to understand the analgesic mechanism of acupuncture. Their study showed that development of acupuncture-induced analgesia took 15 to 20 minutes [13]. Endogenous opioid peptides (EOP) appeared to be the major mediators of acupucture's analgesic action as naloxone an opioid receptor antagonist, abolished the effect [14]. In addition, elevated levels of EOPs in plasma and cerebro-spinal fluid following electro-acupuncture (EAA) in humans have been reported. Activation of opioid receptor has been found to be associated with frequency of EAA; viz. low frequency (2 Hz) activated mu- and delta opioid receptors due to the release of endomorphin, enkephalin and beta-endorphin and high frequency (100 Hz) activated kappa opioid receptor due to release of dynorphin in the spinal cord [15]. Instantaneous pain relief in patients following insertion of acupuncture needle has also been observed, which appears to be due to conditioning stimulation of diffuse noxious inhibitory controls (DNIC), whereby application of a noxious stimulus to anywhere in the body could immediately suppress pain transmission in trigeminal neurons and/or the dorsal spinal horn [16, 17]. Activation of thin afferent A-delta and C fibers derived from nociceptors underlie DNIC as these fibers are responsive to mechanical, thermal and chemical stimuli [18]. These nociceptors are distributed all throughout the body

whose afferent inputs resemble the functioning of polymodal receptors.

In case of neuropathic pain, acupuncture efficacy has been shown to be associated with the activation of ephrin-B/EphB signalling in preclinical setting [19, 20]. Ephrins are membrane-bound ligands of Eph receptor tyrosine kinases and this system modulates synaptic efficacy in the spinal cord. Repeated acupuncture has been shown to increase mRNA levels of ephrins and EphBs in the dorsal horn of spinal cord. Ephrin-B3 protein expression is increased after acupuncture and correlates with therapeutic efficacy of the treatment. These reports suggest that alleviation of neuropathic pain by acupuncture involves spinal ephrin-B/EphB signalling [15, 21].

Acupuncture and pain management

In the United States, 3 million people have been reported to receive acupuncture therapy in 2007 for relieving various kinds of pain such as low back pain, joint pain, neck pain and headache [22]. The major reason for seeking acupuncture therapy by the patients was lack of confidence on conventional medical care in relieving pain. Indeed, conventional physicians often suggest seeking acupuncture to their patients. Among the users, 46% felt acupuncture to be very effective, 26% felt it to be somewhat effective and 28% felt it to be little or not effective [23].

Efficacy of acupuncture in different types of pains

Research from China showed significant efficacy of acupuncture in ameliorating back pain however studies done in other parts of the world failed to corroborate it [24]. Several high quality randomized clinical trials (RCT) have generally concluded that acupuncture was effective in relieving back pain compared with no treatment and comparable to usual care for back pain [25]. A meta-analysis that considered 22 RCTs found a small but statistically significant effect of acupuncture in reducing chronic low back pain when administered for more than 3 months compared with sham acupuncture group. However, the effect of acupuncture was not significantly better than massaging and other active treatments [26]. A randomized and double-blind parallel group trials carried out at multiple centres (the German Acupuncture Trials, GERAC) showed that at 6 months both acupuncture and sham acupuncture groups had statistically significant pain alleviation compared with conventional [27]. Furthermore, a randomized control trial compared patients under usual care, sham acupuncture and acupuncture, and observed that both acupuncture and sham acupuncture groups were significantly better in terms of pain alleviation compared with usual care [28]. From these reports, it appears that sham acupuncture is a controversial procedure when an appropriate control method is sought.

In a large RCT consisting of patients with motion-related neck pain, 1880 were randomized to acupuncture and 1886 to routine care groups and treatments were administered for 3 months. The study showed that significant improvements in clinically relevant pains and disability in the acupuncture group compared to routine care group, and this beneficial effect persisted for 6 months [29]. In addition, effect of acupuncture was tested in in reducing the frequency of headaches in subjects with tension-type headache. Two large unblinded studies reported that, adding acupuncture in the short-term (3 months) to routine care or acute headache treatment decreases the frequency of headache [30, 31]. In a meta-analyses consisting of five trials showed statistically significant effect of acupuncture albeit small over sham acupuncture in tension-type headache. Authors found the evidence for the effect of acupuncture in reducing the frequency and intensity of headache to be insufficient, however, recommended considering this otherwise safe non-pharmacological tool in patients [32]. In a small randomized, controlled trial consisting of 74 patients with chronic daily headache under the medical management of neurologists reported that acupuncture added to ongoing medical management resulted in significant reduction headache and improved the quality of life over the group that received only medical management [33].

OA and current treatment regimens

Synovial joints such as in knee and hip are lined by articular cartilage. Articular cartilage promotes load transfer for frictionless joint movement. Chondrocytes in articular cartilage produce type II collagen and proteoglycans which

are the major extracellular matrix constituents and OA is caused due to focal degradation of articular cartilage due to abnormal activation of chondrocytes and resident mesenchymal stem cells [34, 35]. Hyaluronic acid (HA) is a component of articular cartilage and performs the function of a lubricant under the condition of shear stress and acts as a shock absorber during compressive stress. In response to the degradation break down of extracellular matrix of articular cartilage new bone formation (osteophytes) occurs at joint margins via the deposition of type X collagen and type IIA procollagen proteins that are not part of articular cartilage. As a result of abnormal protein deposition, effortless gliding of joints is prevented causing stiffness and also give rise to chronic pain.

OA of knee is the most common type seen in adolescents. OA of knee could result in decreases in the levels as well as truncation of endogenous HA [36]. HA is common treatment to alleviate the symptoms of OA of knee by inhibition of cartilage degrading enzymes and local inflammation [37]. HA is administered by intra-articular injection [38]. A number of HA products are approved for clinical use by the United States Food and Drug Administration.

A systematic review and meta-analysis study was performed to investigate the efficacy of either platelet-rich plasma or HA in knee OA keeping Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) outcome. HA was effective in the treatment of OA however platelet rich plasma was even better [39]. HA has been shown to have equal efficacy with corticosteroid in knee OA in short-term (1 month) and better effect than corticosteroid in long-term treatment [40]. In yet another meta-analysis HA was compared with non-steroidal anti-inflammatory drugs (NSAIDs) for alleviation of OA-induced pain and data of five RCTs were considered. Analysis suggested that HA had comparable efficacy with NSAIDs. However, considering the better safety profile of HA over NSAIDs, particularly among the elderly population who are at a greater risk of systemic adverse effects of NSAIDs, HA appeared preferable alternative to NSAIDs [41]. In a meta-analyses consisting of 29 studies that included 4,866 unique subjects and divided into two groups (2,673 HA and 2,193 saline), the treatment effects between 4 and 26 weeks were studied. When knee pain and function were compared with pre-treatment values, HA group showed significant reduction in pain and improvement in function compared with saline, whereas there was no significant difference in adverse events between the two groups [42].

Paracetamol is used as the first line of pharmacological intervention for pain relief in OA as it has better safety profile over non-steroidal anti-inflammatory drugs (NSAIDs) [43]. However, a placebo controlled, double-blind and parallel group trial for assessing analgesic efficacy of paracetamol (4 g/day) in knee OA was carried out in 779 patients (drug arm = 405 and placebo = 374) for 6 weeks, and the study failed to find a statistically significant symptomatic relief, which has put a big question mark to the use of paracetamol [44]. The second line of pharmacological intervention is NSAIDs that are used for relieving pain and mitigating joint stiffness in OA. However, safety concerns of NSAIDs, particularly gastro-intestinal safety preclude their use in recent years. Vioxx was withdrawn from the market due to risks of cardiovascular infarcts and this withdrawal also led to marketing restrictions for other inhibitors of cyclooxygenase-2, so called coxibs. Overall, NSAIDs are considered to offer short-term symptomatic relief of OA pain and OA-related stiffness. Therefore, considering the safety concerns with NSAIDs, there is a void in pharmacological intervention for OA. In terms of alternative therapies, ultrasound and short-wave do not enjoy convincing scientific evidence for the management of OA.

Acupuncture and OA

According to European League Against Rheumatism (EULAR) review, acupuncture and transcutaneous electrical nerve stimulation (TENS) fall in the category of class 1B, i.e. under the same evidence level as enjoyed by coxibs and paracetamol [45]. Also, the statistical power of studies conducted for acupuncture is comparable with pharmacological interventions. Pain reduction in patients with knee OA has been described in several studies. There are five high quality and four moderate quality studies that reported significant pain reductions and two studies failed to find significant pain reduction in patients with OA of knee [46-54]. Among the studies showing successful pain reduction by acupuncture, only one used the WOMAC pain scale [50] and the rest used either visual ana-

Table 1. Summary of RCTs on OA of knee and acupuncture

RCT type	Intervention type	Outcome measures	Results	Risk of bias
DB [99]	EA	Pain, function	√, ×	High
DB [100]	TA	Pain, function	√, √	High
DB [101]	TA	Pain (1), function (2)	×, ×	High
DB [52]	TA	Pain, function	√, ×	High
DB [54]	TA	Pain, function	√, √	Moderate
DB [47]	TA + diclofenac	Pain	√	High
PB [53]	TA	Pain, function	√, √	Moderate
PB [49]	EA	Pain, function	√, √	Moderate
PB [48]	TA	Pain and function	√, √	High

Pain was assessed by either VAS or WOMAC score; function was assessed by gait analysis, walk time or workdays lost. DB, double blind; PB, patient blind; EA, electroacupuncture; TA, traditional acupuncture; √, effective; ×, not effective.

logue scale (VAS) or numeric rating scale (NRS). In addition, several studies have shown that acupuncture could significantly improve joint flexibility and physical function of patients with OA of knee [46-49, 54]. Majority of these studies used the WOMAC pain assessment scale but only one of these studies performed gait analysis as physical function outcome [54]. A summary of various RCTs on OA of knee and the effect of acupuncture administration have been provided in **Table 1**.

A clear advantage of acupuncture over the pharmacological interventions is that it is safe. In addition, unlike clinical trials with pharmacological interventions being sponsored by pharmaceutical industries, acupuncture trials were sponsored by independent agencies, thus mitigating the chance of conflicts of interest [55].

RA and current treatment regimens

RA is an autoimmune disease which is characterized by joint destruction due to infiltration of immune cells from blood stream which participate in various inflammatory processes. The onset of inflammatory process activates osteoclast precursor cells to become differentiated osteoclasts resulting in the destruction of joint bones [56]. NSAIDs such as ibuprofen, ketoprofane and naproxen are given to ease arthritis pain and reduce inflammation. As these drugs could cause gastritis, patients who are at a high risk of gastric ulcer should be given coxib drugs, COX-2 inhibitors. To aggressively control RA inflammation, synthetic corticosteroids including prednisone, prednisolone and methyl prednisolone are prescribed.

In last several years, so called disease-modifying anti-rheumatic drug (DMARD) classes have emerged that include several small molecules such as methotrexate, hydroxychlorquine, sulfasalazine, cyclophosphamide and azathioprine [57, 58]. In addition, there are target specific biologic treatments which also fall under DMARD and include monoclonal antibodies against tumor necrosis factor and interleukin-1 to neutralize the functions of these inflammatory cytokines that underlie the pathogenesis of RA [59]. IL-6 signaling is another cause of RA pathogenesis and for which tocilizumab (actemra), an IL-6 receptor antagonist is used. Among multiple kinases, Janus kinase (JAK) has critical roles in the RA pathology. Tofacitinib, a small molecule targeting JAK, inhibits its signalling to achieve anti-inflammatory effects. Compared to NSAIDs, corticosteroids and coxibs, DMARDs are safer and more effective in treating RA [60]. However, still there are a number of safety concerns associated with DMARDs including increased risk of infection, cytopenia and hepatotoxicity, all of which are reported for methotrexate. Mycobacterium and viral infections have been associated with TNF inhibitors [59]. Risk of serious infection has also been reported with IL-1 and IL-6 inhibitors [61].

Acupuncture and RA

Effect of acupuncture in relieving pain in RA has not been rigorously investigated. Although a large number of studies reported on the efficacy of acupuncture in RA, serious methodological concerns limit their interpretation. Four randomized placebo controlled trials were included for review, of which 3 had optimal quality and 1 had moderate quality [62-65]. In a RCT of 20 patients with seropositive RA, 1 session of electroacupuncture significantly reduced knee pain [65]. However, another randomized crossover study consisting of 56 RA patients failed to find any significant effect of traditional acupuncture in pain relief or inflammation compared to sham acupuncture group (placebo) [64]. The authors of this study discussed that given the patients in their study had established erosive rheumatoid disease (at a more advanced stage), response to acupuncture could be limited, and have predicted that patients who are at the early-erosive stage could

Table 2. Summary of RCTs on RA and acupuncture

RCT type	Intervention type	Outcome measures	Results
DB [62]	EA/TA	Pain, functions (1, 2)	√, √
DB [64]	SPA	Pain, functions (1, 2, 3)	×, ×, ×
DB [63]	TA	Pain, functions (1, 2, 3, 4)	×, ×, ×, ×

Pain was assessed by either VAS or WOMAC score; function was assessed by 1 (tender joint count), 2 (swollen joint count), 3 (global assessment) and 4 (inflammatory markers). DB, double blind; PB, patient blind; EA, electroacupuncture; TA, traditional acupuncture; SPA, single point acupuncture; √, effective; ×, not effective.

be responsive. A systematic review of included these two studies and concluded these to be of medium quality study due to limitations related sample size (small) and methodological concerns. Also, these studies failed to find any efficacy of acupuncture on inflammatory measures such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and number of swollen or tender joints. When 2 well-designed (double-blind, randomized and placebo-controlled) studies were considered, one found significantly improved tender joint and pain by traditional acupuncture [62] but the other failed to find any effect of acupuncture over placebo [63]. A summary of well-designed RCTs on RA and the effect of acupuncture administration have been provided in **Table 2**.

Acupuncture and gouty arthritis

Hyperuricaemia (blood uric acid > 6.5 mg/dl) results in gout, a disease that causes significant morbidity. Clinical management of gout requires urate-lowering drugs (allopurinol and probenecid), NSAIDS and glucocorticoids. Pharmacological interventions for gout suffer due to lack of physicians' adherence to quality indicators (QI) of care dispensed to patients. One study reported that QIs related to medication management (treatment adherence to uric acid-lowering medicines and NSAIDs) to be inadequate and thus requires improved intervention for better therapeutic outcome [66]. Also, suboptimal care in terms of medication use and response monitoring in patients with gout diminish therapeutic outcomes [67].

A systematic meta-analysis included 10 studies involving 852 patients of gouty arthritis where effectiveness of acupuncture was considered not only with VAS but also lowering of uric acid level. In addition, comparison of acupuncture efficacy was made with Western medicine and the overall finding was that acupuncture treatment was effective in decreasing blood uric acid and improving the overall quality of life [68].

Acupuncture and osteoporosis

One of the foremost manifestations of osteoporosis is pain. The commonest type of osteoporosis pain is encountered due to spinal compression fracture. Pain can be felt due to simple movement and carrying loads of household items. Conservative pain management approaches include NSAIDs, narcotics, nerve blocking agents and anti-inflammatory medications. Bisphosphonates, the first line of osteoporosis therapy, which act by suppressing osteoclast function has been shown to decrease bone pain. In a randomized trial on 3889 postmenopausal women (mean age 73 years) received the injectable form of bisphosphonate, zoledronic acid (5 mg) as a once-yearly infusion for three consecutive years showed significant reduction in the risk of vertebral, hip and long bone fractures, and reduction in back pain compared with the placebo group [69]. Human parathyroid hormone (1-34) or teriparatide which is the only osteoanabolic therapy available for osteoporosis has been found to be more effective than bisphosphonates in relieving osteoporotic pain. In a multicentre, prospective and observational study carried out in eight European countries, 18 months teriparatide treatment to severely osteoporotic postmenopausal women and who were prior treated with bisphosphonates, not only reduced the incidence of fracture but also back pain and improved health-related quality of life [70]. In a head to head comparison between teriparatide and bisphosphonates, the former was associated with reduced back pain and better life quality [71]. However, the study was sponsored by Eli Lilly, the manufacturer of teriparatide. However, the major limitation with oral formulations of bisphosphonates is GI toxicity which leads to significantly decreased treatment adherence [72]. Regarding teriparatide, the maximum allowable treatment time is 2 years and bone loss takes place soon after its cessation. Therefore, an alternative long-term therapy is desirable for mitigating osteoporosis pain.

In a preclinical rat model of osteopenia, the effect of acupuncture on bone biomechanical strength and histomorphometry was studied.

Osteopenia was induced by bilateral ovariectomy (OVX) and sham-operated rats served as ovary intact group. To one OVX group, acupuncture was performed by needling on Pishu (BL20) and Shenshu (BL23) for 15 min daily for 16 weeks. To one OVX group of rats, sham acupuncture was applied. At the end of the study (16 weeks post-surgery), acupuncture administered OVX rats showed significantly better femur biomechanical strength and trabecular microarchitecture over sham-acupuncture administered OVX rats. These data suggested that acupuncture could potentially prevent OVX-induced loss of trabecular architecture and biomechanical strength [73].

In six-month old male senescence-accelerated mice strain P6 (SAMP6), acupuncture at Shenshu (BL23) point was administered daily for 8 weeks. Acupuncture treatment markedly increased the lowered serum testosterone level that is associated with control SAMP6 mice (sham acupuncture group). Also, trabecular microarchitecture and bone biomechanical strength were increased by acupuncture in SAMP6 mice. These data suggest that acupuncture is effective in mitigating loss of bone architecture and strength caused by deficiency of gonadal hormone as observed in aged humans [74].

There is no study on the effect of acupuncture in patients of post-menopausal osteoporosis. Common fractures in post-menopausal osteoporosis are spine, hip and wrist. Pain from these fractures is a major cause of morbidity. Unlike, pain in OA or RA, effect of acupuncture in fracture-related pain in osteoporotic patients in the form of high quality RCT is lacking. According to classical traditional Chinese medicine, bone function is regulated by kidney (so called Nei Jing theory). This thesis predicts that improving kidney function by acupuncture will improve bone health in osteoporosis [75]. Indeed acupuncture has been shown efficacy in a variety of kidney diseases including chronic kidney disease, uremic pruritus, end-stage renal disease [76, 77], kidney inflammatory disease and macrophage-mediated glomerulonephritis [78].

Acupuncture and other musculoskeletal pain

When acupuncture for different musculoskeletal pain was subjected to meta-analysis and meta-regression of sham-controlled RCTs, it was found to be more effective than sham treatment in chronic neck pain and shoulder pain (evidence level was graded as high), chronic low back pain and myofascial pain (evidence level moderate) and OA (evidence level low). There was no evidence for better efficacy of acupuncture over sham treatment for arm pain, RA and acute neck and low back pain [79]. When musculoskeletal disorders of extremity is considered, several studies have reported that acupuncture was better than oral steroid and vitamin B1 and B6 supplement in bringing about relief from pain in carpal tunnel syndrome [80-83]. Acupucture was also found to be better than exercise in Achilles tendinopathy [84]. However, efficacy of acupuncture treatment in patellofemoral pain and plantar fasciitis is questionable [83].

Acupuncture and bone cancer pain

Skeletal metastases are frequently observed in cancers that are in advanced stages and include breast, lung or prostate cancer, and multiple myeloma. These cancers are generally metastasized in the axial skeleton [85, 86]. In cancer-induced bone pain, often spontaneous breakthrough pain is experienced by the patients for whom high doses of medications are required to alleviate pain. This type of bone pain is also unique as central sensitization and upregulated nociceptive system make it unbearable. In cases of breast and prostate cancers, post-metastatic survival is long (measured in years) and therefore reducing pain to preserve normal activity is an important aspect of maintaining good life quality.

Current pain management in bony metastases include the use of opioids, bisphosphonates and radiotherapy. Although these therapies offer some pain relief but are also associated with undesirable side effects. For example, high doses of opioids cause nausea, constipation and drowsiness. Injectable bisphosphonates (zoledronic acid) causes GI disorders and osteonecrosis of jaw [87].

Given its analgesic effect, acupuncture holds potential to becoming an adjunct strategy for pain relief in cancer-induced bone metastases. Acupuncture is already in wide use as a palliative care for a variety of cancers, however, the levels of evidence is not high quality [88-90]. In

a preclinical study, prostate cancer cells were inoculated in tibia of rats that resulted in the development of thermal hyperalgesia. Electroacupuncture treatment in these rats significantly reduced hyperalgesia evidenced from increasing paw withdrawal latency that was associated with suppression of an inflammatory cytokine, interleukin-1β expression [91]. In another study, inoculation of prostate cancer cells into rat tibia caused bone cancer and EA treatment significantly increased paw withdrawal latency and inhibited preprodynorphin and dynorphin levels in the spinal cord [91]. As spinal dynorphin pro-nociceptive [92], its suppression by EA explained the mechanism of EA-induced pain relief in bone cancer.

A hospice in U.K. assembled data of fifteen patients over 12 months which showed that ten patients experienced pain relief. However, detail protocol was lacking in this report [93]. In a study involving 156 cancer patients over five years, acupuncture was found to offer pain relief in patients with bone pain [94]. However, no details on the type of patients with bone pain who were benefitted from acupuncture were available. A systematic review on the effect of acupuncture in cancer-related pain provides an equivocal data on pain relief and no study on patients with bone cancer pain was included [95]. Presently, it appears that there is no streamlined acupuncture protocol for effective pain alleviation in patients with bone cancer.

Regulatory approval, acupuncture therapists, safety and cost

In the U.S. over 3 million adults receive acupuncture for chronic pain and majority of these cases involve musculoskeletal sites [96, 97]. Acupuncture has significant therapeutic efficacy in mitigating lower back pain and the cost of treatment is low [98]. The cost of treatment typically ranges from U.S. $30-100 and the procedure could take from days to weeks depending on the nature of pain.

In 1996, the U.S. Food and Drugs Administration approved acupuncture needles for use by license holders. Also, regulatory requirement requires manufacturer to label acupuncture needle for single use only. In the U.S., patients could search for licensed acupuncturist at the site http://www.medicalacupuncture.org/For-Patients/Articles-By-Physicians-About-Acupuncture/NCCAMAcupunctureResources. However, advocacy for acupuncturists to whom patients are referred from this site should be taken into consideration. The American Academy of Medical Acupuncture and the National Acupuncture and Oriental Medicine Alliance provide list of acupuncturists to patients who need it in the U.S. Relative cases of complications from the use of acupuncture are few considering its popular use surpassing millions of cases. However, serious adverse effects of wrongly dispensed acupuncture include infections and organ damage. Major health insurance companies in the U.S. cover the cost of acupuncture for the last two decades.

Summary and future direction

Acupuncture serves as a complimentary intervention for chronic painful conditions arising from bone and joint diseases including OA, RA and gout. Analgesic effect of acupuncture in neck and back pain is well documented. The evidence base in this regard is high quality and provides rationale for providing this therapy by mainstream care providers to patients. Acupuncture has also been tested as an adjunct to clinically used therapies to alleviate pain and reduce stiffness associated with OA and RA, thus raising improvement of quality of life over clinically used monotherapy. Regarding pain associated with post-menopausal bone loss, the quality of clinical studies is low grade and thus calls for high grade trials. Overall, with respect to chronic pains including those arising from bone and joints, acupuncture has established itself as a referral option which is devoid of safety concern. However, claims pertaining to disease modifying effect of acupuncture in OA and RA require much closer look and high quality trials. In addition, improvement in quality of life due to the analgesic effect of acupuncture also needs to be re-visited as stiffness of joints in RA and OA limits mobility and whether acupuncture could alleviate stiffness and thus promote effortless mobility. Also, very little is known about the acupuncture dosage (frequency and time) in terms of its analgesic effect for various diseases of bone and joint. Filling these gaps would further enrich our knowledge about acupuncture to provide better care for patients suffering from chronic pains from diseases of bone and joints. Therefore, more high quality clinical studies on the effect of acupuncture on

diseases of bone and joint pains with respect to pain mitigation, joint flexibility and ease of movement and disease modifying outcomes are required to recommend this treatment modality to patients.

Disclosure of conflict of interest

None.

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