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Chapter 8

Placenta Therapy: Its Biological Role of Anti-Inflammation and Regeneration

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.79718

Abstract

Human placental extract has been used to treat fatigue, postmenopausal symptoms, wound healing, and growth retardation in Korea. Combined with acupuncture therapy, placental extract extends its therapeutic limit to pain control. Recently, we have reported acupuncture point injection (API) with placental extract modulated inflammation-involving pain symptoms in chronic pain diseases. In order to rehabilitate patients suffering from chronic pain and restricted joint mobility, placental extract was injected into acupuncture points localized on the joints, surrounding muscles acting in concert with the joints, and paravertebral muscles affecting the innervation of the joints. Here, we describe the pathology of pain syndromes including neck pain, back pain, shoulder pain, knee arthritis, fibromyalgia, and complex regional pain syndrome and propose methodology of APIs with placental extract in treating these pain diseases.

Keywords: placental extract, acupuncture point injection, regeneration, anti-inflammation, neck and back pain, shoulder pain, knee arthritis, fibromyalgia, complex regional pain syndrome

1. Introduction

The human placenta is a unique organ that connects the developing fetus to the uterine wall. The placenta provides nutrient uptake, thermo-regulation, waste elimination, and gas exchange to growing fetus via the mother's blood supply. Since the placenta is a provisional organ, it becomes a salvage material after delivery. For decades, clinicians and researchers work on the application of the placenta for therapeutic purposes. The types of placental preparation used in the studies are fragments of placental tissue, amniotic and chorionic

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membranes, umbilical cord, amniotic fluid, placental extracts, and cord blood stem cells. Methods of application widely vary from subcutaneous, intramuscular, intravenous, intraoperative, biocovers, and substitutive material to oral administration [1–3].

Research on human placental extract began to thrive from the description on the method of its preparation by Russian ophthalmologist Filatov [4]. Filatov initially observed that grafting-preserved human corneas had better clinical outcomes than freshly isolated ones. He convinced that isolated tissues readjusted themselves to develop biogenic stimulators under unfavorable environmental factors. He advocated the principle of therapeutic tissues which could exhibit curative effects by adapting themselves to the tissues affected by the pathological process. Since placenta is a storehouse of potent biogenic stimulators, the application of placental extract ranges from immunology, stem cell research, genetics, and cancer research to tissue engineering. Placental extracts were demonstrated to contain wide range of peptides, proteins, minerals, amino acids, nucleotides, carbohydrates, and steroid hormones.

Experimental evidence has accumulated on the therapeutic effects of placental extracts. One of the most important roles of the placenta is to protect the embryos from oxidative stress, and therefore, placental extract has antioxidative properties [5]. Antioxidant properties of placental extract are usually associated with the protein components, especially alpha-fetoprotein [6]. Injecting placental extract to a wound margin [7] or applying placental extract topically to chronic nonhealing wounds [8] promoted healing of injured tissues. This mechanism appears to be related to an increase in transforming growth factor-beta (TGF-β) in the early phase of wound healing and vascular endothelial growth factor (VEGF) in the late phase [8]. The regeneration of sciatic axons by placental extract injection was validated by increased synthesis of regeneration-related protein factors such as GAP-43 and Cdc2 [9]. Application of placental extract in menopausal disorders allowed reducing the number of hot flushes and normalized hormone profiles [10]. Experimental animal model studies showed that placental extract decreased symptoms of fatigue and increased resistance to physical stress [11]. Placental extracts were also demonstrated to have anti-inflammatory effects in both animals and humans. In adjuvant-induced polyarthritic rats, injection of placental extract was demonstrated to alleviate arthritic symptoms including joint destruction and expression profiles of inflammatory cytokines [12]. Intra-articular injection of placental extract reduced deformity of knee joints and inhibited matrix metalloproteinase-2 and -9 activities of cartilages of osteoarthritic knee joints in rats [13].

Recently, acupuncture point injection (API), an injection at an acupuncture point of a small amount of medicinal solution, has been widely used for the treatment of various pain syndromes in China and Korea. API is derived from intramuscular injection in Western medicine and then gradually integrated into traditional Chinese medicine [14]. The medical agents administered in acupuncture points are thought to play a synergistic effect with acupuncture point stimulation, and this method is believed to have a more sustained effect than the traditional acupuncture needling or simple intramuscular injection [15]. API is reported to increase cerebral blood flow, improve adjuvant arthritis, and have analgesic and anticoagulatory effects [16–18]. In clinical studies, API improved cervical disc herniation, knee osteoarthritis, and low back pain [19–21]. Here, we intended to propose an API with placental extract in treating chronic pain syndromes. The mechanistic explanation of acupuncture points employed in the treatment of respective pain syndromes is also explored.

http://dx.doi.org/10.5772/intechopen.79718

2. Preparation of placental extract

Placental extracts are classified to several types depending on the methods of its preparation. Initial extraction was done by employing the Filatov's procedure [4] but an acid-hydrolyzed water extraction is prevailing in Korea due to its high recovery of functional macromolecules from placental tissues. Human placentas, collected upon full-term delivery, were tested for human immunodeficiency virus and hepatitis B and C viruses. They were cut into pieces, defatted with acetone, and extracted with water through pepsin and hydrochloric acid-catalyzed hydrolysis. Resulting placental extract was tested for germ-free, antihistamine, and endotoxin-free under the regulation of Korean Food and Drug Administration. The final placental extract product was sterilized, packaged at 2 ml/ampule, and approved for injection for human by subcutaneous and intramuscular. Insoluble macromolecules, such as polysaccharide, polynucleotide, etc., were excluded during the manufacturing processes. The trade name of the extract, "Laennec", is provided from Green Cross Ltd. (Yongin, Korea). Kong et al. [22] analyzed and reported the levels of cytokines and hormones of Laennec by using automated biochip array technology.

3. Treatment of pain based on anti-inflammation and regeneration

Musculoskeletal disorders are the most frequent cause of disability in the modern world, and the prevalence of these diseases is rising at an alarming rate. The most prominent reason for loss of joint mobility and function is chronic pain, which leads to impaired quality of life. Current therapies to alleviate pain have limited effectiveness, and some drugs produce unwanted negative side effects, thereby precluding their long-term use.

Nociceptive receptors are located throughout the joint. It has been identified in the capsule, ligaments, menisci, periosteum, and subchondral bone. If a noxious mechanical factor or inflammatory mediator is applied to the joint, the firing rate of the afferent nerve increases dramatically, and the central nervous system interprets this nociceptive activity as pain [23]. Transient pain is induced and serves as a physiological warning at brief, high-intensity stimuli, which produce little or no tissue damage. However, in chronic pain conditions, there may be spontaneous pain, as well as intermittent pain, which is induced by persistent inflammation from structural damage or functional degeneration. Chronic pain is also associated with complex changes in peripheral and central signal processing [24].

It is accepted that inflammation and the inflammatory response play pivotal roles in the occurrence, as well as progress of pain. The biochemical mediators of inflammation include cytokines, neuropeptides, growth factors, and neurotransmitters. Irrespective of the type of pain whether it is acute or chronic pain, peripheral or central pain, nociceptive or neuropathic pain, the underlying origin is inflammation and inflammatory response. Activation of pain receptors, transmission of pain signals, and modulation of neuroplasticity all belong to a continual spectrum of inflammation and inflammatory response.

Every pain syndrome has an inflammatory profile consisting of the inflammatory mediators that are present in the pain syndrome. The inflammatory profile may have variations from

one person to another and may have variations in the same person at different times. Various symptoms of pain syndromes are attributed from corresponding inflammatory profiles of discrete pain syndromes. The key to treat pain syndromes is inhibiting the production of inflammatory mediators at the same time regenerating injured or degenerative tissues. The term "regeneration" is used to describe the phenomena that allow an organism to reconstitute the structure damaged by injury and recover the functional homeostasis. A successful outcome is one that results in less inflammation, more regeneration, and thus less pain.

4. Anti-inflammatory effects of acupuncture point injection with placental extract

Acupuncture has been used in the treatment of several diseases for at least 5000 years in Asia. In the western society, acupuncture has become a central part of complementary medicine. An increasing number of patients, especially those suffering from chronic diseases, are seeking acupuncture treatment. The widespread application of acupuncture includes the treatment of infections, inflammatory diseases, autonomic dysfunction, psychological disorders, musculoskeletal diseases, and many other illnesses [25].

The neural activation by acupuncture was investigated by many researchers. With the stimulation of vision-related acupuncture points, visual cortices of the brain were found to be stimulated [26]. Liu et al. [27] and Li et al. [28] reported that the C-fiber rich afferents of the deep tibial nerve coincided with acupuncture points, implying rich distribution of nerve fibers/reflex complexes at acupuncture points. Abraham et al. [29] also proved that the acupuncture points contained a significantly higher number of transient receptor potential vallinoid type 1-positive Aδ- and C-fibers as compared with nonacupuncture points. Gao et al. [30] demonstrated that the enhancement of gastric motility induced by acupuncture point ST36 stimulation was mediated by N-methyl-D-aspartate receptors.

In acupuncture, the insertion of needle induces marked changes close to the needle in all different tissues that are penetrated. These peripheral events might improve tissue function through dilation in the skin due to axon reflexes [31]. Additional activation can be obtained through manipulation of the needle or electro-stimulation at different frequencies. Studies have shown that manual acupuncture (back-and-forth motion or up-and-down motion) or electrical stimulation in specific frequencies applied to acupuncture points can facilitate the release of specific neuropeptides in the central nervous system [32]. This activation is demonstrated to elicit profound physiological effects and even activate self-healing mechanisms [33]. Although the effect of manual acupuncture or electro-acupuncture is comparative to the effects of nonsteroidal anti-inflammatory drugs and opioid analgesics [34], maintenance of needles might be cumbersome, particularly in agitated animals. In order to overcome this disadvantage, other techniques might be used for stimulation of acupuncture points.

Acupuncture point injection (API) is a new acupuncture technique which combines acupuncture and medication. API is widely used to enhance and prolong the effect of stimulation of acupuncture points [35]. API with placental extract can be used to control pain syndromes

due to anti-inflammatory effects from each member. Numerous uncontrolled trials, as well as a limited number of controlled trials, have been published after short-term or long-term use of acupuncture in the treatment of inflammatory diseases. The direct and indirect effects of acupuncture on regulation of inflammatory mediators such as neuropeptides, cytokines, and vasoactive substances have been assessed [36]. Even though there are some pitfalls such as relatively small number of patients and incompletely described methodological procedures, the results clearly show a beneficial effect of acupuncture in the reduction of symptomatic inflammatory response. As well, anti-inflammatory effects of placental extracts were fully evaluated. Porcine placental extract was shown to protect the contact hypersensitivity of skin by modulation of immunoglobulin E production [37]. Animal model studies showed that placental extracts reduced the concentration of free radicals, inflammatory cytokines interleukin-6 (IL-6), tumor necrosis factor (TNF), and interleukin-1 (IL-1) at the same time increasing the colony formation of progenitor cells in vitro [38]. Clinical trials of API with placental extracts showed anti-inflammatory effects in pain diseases. Injection of placental extract to acupuncture points ameliorated various inflammation-associated symptoms of complex regional pain syndrome [39, 40]. In osteoarthritic patients, API with placental extract improved daily working hours, reduced knee joint swelling, and abated pain [20].

5. Regenerative effects of acupuncture point injection with placental extracts

Regenerative medicine has the potential to heal or replace tissues and organs damaged by age, disease, or trauma. The current therapy of transplantation of intact organs and tissues to treat organ and tissue failures suffers from limited donor supply and often severe immune complications. These obstacles may potentially be bypassed through the use of regenerative medicine strategies. The field of regenerative medicine encompasses numerous strategies, including use of materials and de novo generated cells, as well as various combinations. Regenerative medicine effectively replaces missing tissues both structurally and functionally, thus contributes to tissue healing. The body's innate healing response may also be leveraged to promote regeneration at the time of regenerative procedure [41].

Placental extracts are obtained by lysing human placental tissues collected from full-term delivery. The extracts do not contain cells but are rich in a wide range of proteins, minerals, amino acids, and steroid hormones. Placenta synthesizes a number of hormones, such as estradiol, progesterone, and chorionic gonadotrophin, which regulate growth and development of the fetus during pregnancy so that placental extracts have the impact on proliferation. Data indicate that placental extracts stimulate proliferation and regenerative processes in various systems. The significant increase in tensile strength and tissue DNA in the animals given human placental extract indicates the extract-induced marked collagen synthesis [42]. Human dermal fibroblasts showed an increased proliferation after treatment of human placental extract [43]. Placental extracts were also shown to enhance the proliferation of cord blood cells in vitro [44]. Animal model studies proved that the placental extract promotes fibrogenesis, neoangiogenesis, and epithelialization [8].

Acupuncture has been used to treat injured tissues and recover the degenerative functions. Experimental results have revealed the positive roles of acupuncture on injury-induced regeneration. Electro-acupuncture was shown to promote the differentiation of endogenous oligodendrocyte precursor cells into oligodendrocytes in the demyelinated spinal cord in rats [45]. In a rat tendon healing model, mechanical stimuli by acupuncture stimulation at the juxtaposition to tenotomized locus appeared to transduce mechanical stimulation to biological changes [46]. It is proposed that the mechanical stimulation by acupuncture leads to increase in small leucine-rich proteoglycan synthesis by fibroblasts close to the injury sites [47]. Clinical application of electro-acupuncture increased total cell counts, TGF-β1 and basic fibroblast growth factor (bFGF)-positive cell counts, and the mechanical strength of repaired tendon than the control groups received no treatment [48].

API with placental extract has two advantages; acupuncture stimulation *per se* and pharmacological effect of placental extract. As a needle of acupuncture arrives at the site of injured or degenerative locus with placental extract, a regenerative event begins. It is asserted that a combined therapy of acupuncture and placental extract stimulates regeneration more vigorously in injured or degenerative tissues than the separate application does.

6. Methods

Patients with pain syndrome suffer from restricted joint mobility, which leads to impaired quality of life. API with placental extract focuses therapeutic objective on pain control and joint mobilization. A joint is a connection between bones in the body, so that it links the skeletal system into a functional whole. The movable joints such as the knee, elbow, and shoulder are able to withstand compression and maintain heavy loads while still executing smooth and precise movements. According to the earlier work of Melzack [49], trigger points and acupuncture points are the same phenomena in terms of pain though they are discovered independently and labeled differently. This concept was consolidated by Dorsher and Fleckenstein [50], who used a graphic software to evaluate the anatomical relationship between the locations of classical acupuncture points and trigger points. A harmonious movement of joints can be accomplished by an interplay between properly positioned joint and its cognate muscles. The qualified acupuncture points adopted in API with placental extract are ones which are located on the joint, muscles responsible for movement of the joint, and paravertebral muscles modifying the innervation of the joint. There have been reports to support the therapeutic rule of API with placental extract in treating pain syndromes. Intra-articular injection of medication is widely applied to reduce joint pain and increase joint mobility [51]. Trigger points release with injection of pharmacological substances to dynamic motor muscles is used for the accomplishment of proper muscular kinetic chain [52]. Moreover, a higher prevalence of arthritis at other sites is validated in the patients with lumbar spine degeneration [53]. Based on the clinical effectiveness of API with placental extract, we, thus, provide a brief description on the pathology of pain diseases and methodology of API with placental extract in treating these diseases.

http://dx.doi.org/10.5772/intechopen.79718

6.1. Neck and back pain

Neck and back pain most commonly results from injuries to muscles, disks, nerves, ligaments, or facet joints with subsequent inflammation and spasm [54, 55]. Degeneration of disks or joints produces the same symptoms and occurs by aging, previous injury, or excessive mechanical stresses. Herniation of disk tissue produces a profound inflammatory reaction with release of inflammatory chemical mediators especially TNF-α [56]. Subsequent to the release of TNF-α, an increase in the formation of inflammatory mediators such as prostaglandin and nitric oxide as well as phospholipase A2 activation ensues [57]. In sequence, activation of motor nerves that travel from the spinal cord to the muscles results in excessive muscle tension, spasm, and pain. It is accepted that inflammation and the inflammatory response are responsible for neck and back pain both with and without herniated disk [58].

The set of acupuncture points recommended are Ex-HN15, GB21, SI14, and BL10 for neck pain. A sterile 40-mm-long 23 gauge needle is inserted into the acupuncture points at the same time as patients are seated. Ex-HN15 (**Figure 1**), a member of extra channel acupuncture points, is localized on the facet joint between the cervical vertebra 6 (C6) and 7 (C7). From the injury mechanisms during stimulated whiplash, it was revealed that capsular ligament strain reached a maximum at C6-C7 [59]. Through Ex-HN15, 1 mL of placental extract is infused to the facet joint cavity between C6 and C7.

Injection to the trigger point–related muscle areas is a good choice for eliminating shortened sarcomeres including contraction knots. Usually, 1 mL of placental extract is injected to the acupuncture points, while needles are inserted to a depth of 25 mm, which is deep enough

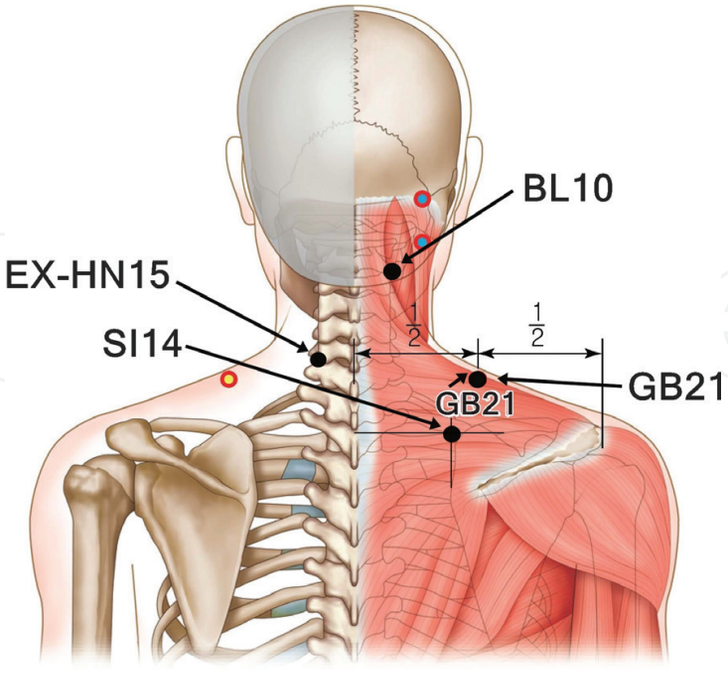


Figure 1. Acupuncture points for treating neck pain.

to penetrate the body of the muscle mass. GB21 (**Figure 1**) is the midpoint of the line on the posterior neck connecting the spinous process of C7 and the outer margin of the acromion [60] and coincides with the trigger point of the upper trapezius muscle. The upper trapezius originates at the external occipital protuberance, the medial third of the superior nuchal line, the ligamentum nuchae, and the spinous process of C7. Thus, tightness or pain in the upper trapezius is associated with range of motion limitation in neck joint. SI14 (**Figure 1**) is located 4.5 cm away from, horizontally, the lower margin of spinous process of the first thoracic vertebrae (T1) [60] and corresponds to the active trigger point of levator scapular muscle. The levator scapula is attached to the posterior tubercles of transverse processes of C1-C4, and its tightness or pain is associated with limitations in upper cervical motion [61]. BL10 (**Figure 1**) is located on the paravertebral region of the neck, at the same level as the superior border of the spinous process of C2, in the depression lateral to the trapezius muscle [60]. Stimulation of BL10 can relieve contraction knots of the semispinalis capitis and appease the muscular tension on the exporting nerve. It was demonstrated that injection to BL 10 enables the tension of the nape of the neck detangled, resulting in relief of pain such as migraine [62].

Acupuncture points BL23, BL25, BL26, and BL30 are recommended for back pain. A sterile needle with 90-mm-long 23 gauges is used for injection of placental extract to the respective acupuncture points. Acupuncture points BL23 (**Figure 2A**), BL25 (**Figure 2B**), and BL26 (**Figure 2B**) are localized on the facet joint of lumbar vertebra at the second (L2), fourth (L4), and fifth (L5) levels, respectively, and lie on the paravertebral muscles including longissimus, rotator, and multifidus. For the percutaneous treatment of low back pain, the entering point of the needle is 2.5-cm lateral from the median line, with a needle depth of 2.5–8 cm.

Meanwhile, the sacroiliac joint is regarded as a potential source of low back pain, affecting 15–30% of individuals with chronic nonradicular pain [63]. The extensive network of

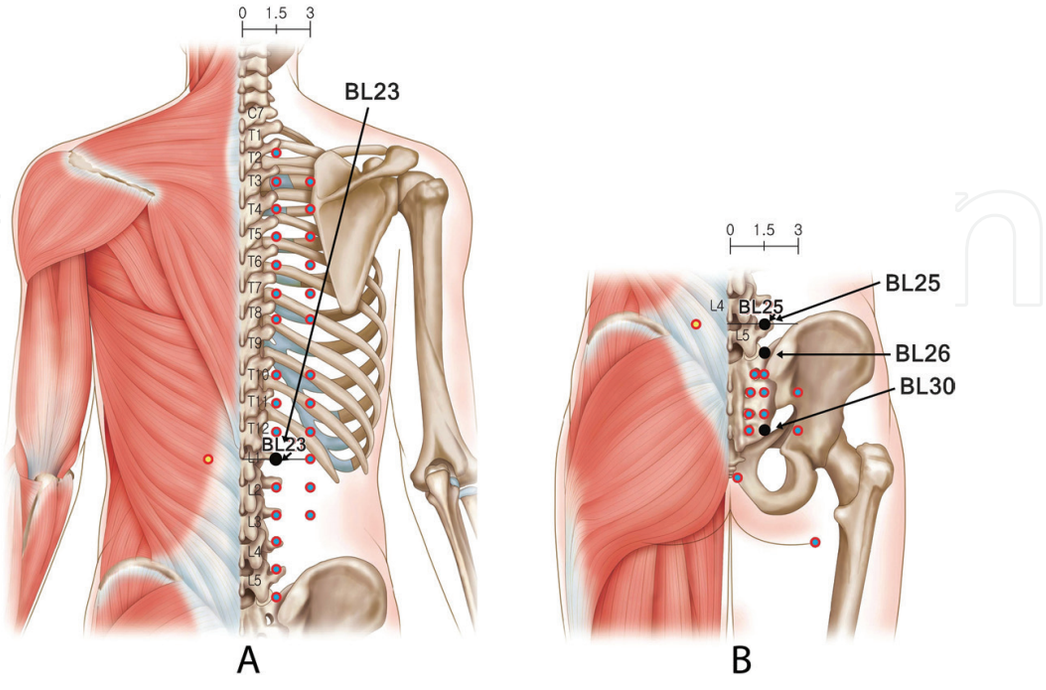


Figure 2. Acupuncture points for treating back pain.

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strong ligaments maintains the integrity of the joint acting as mechanical stabilizers and is also involved with limiting the extent of sacroiliac joint motion [64]. Moreover, posterior pelvic ring ligaments, sacrospinous, and sacrotuberous ligaments significantly contribute pelvic stability. With the use of computational approaches involving finite element modeling, the increased stiffness of sacrospinous and sacrotuberous ligaments was demonstrated to decrease pelvic motion [65]. As acupuncture point BL30 (**Figure 2B**) is localized on the sacrotuberous and sacrospinous ligaments, API with placental extract to BL30 may alleviate stiffness of these ligaments and contribute pelvic stability.

6.2. Shoulder pain

A bursa is a small sac containing fluid that lies between bone and other moving structures such as muscles, skin, or tendons. The bursa allows smooth gliding between these structures by acting as an anti-friction device and shielding the structures from rubbing against bones. Tendons are the thick fibrous cords that attach muscles to bone and function to transmit the power generated by a muscle contraction to move a bone. Almost any tendon or bursa in the body can be affected, but those located around the joint are affected most often. The most frequent causes in shoulder pain are bursitis, tendonitis, rotator cuff tears, and adhesive capsulitis. In one study of 39 patients with rotator cuff diseases, the levels of the cytokine IL-1β were significantly correlated with the degree of pain [66]. In another study, immunohistological staining demonstrated the expression of IL-1β, TNF-α, TGF-β, and bFGF in subacromial bursa derived from the patients suffering from rotator cuff tear [67]. Adhesive capsulitis is characterized by pain, stiffness, and impaired function at the glenohumeral joints. Patients of adhesive capsulitis typically experience onset of shoulder pain followed by a loss of motion especially in the motion of flexion, abduction, and external rotation. As adhesive capsulitis is generally related to a shortening and fibrosis of the joint capsule surrounding the shoulder joint, the contracture of shoulder ligaments actually decreases the volume of the capsule, thus limiting the range of motion [68]. It is likely that limitations in range of motion and pains associated with adhesive capsulitis are not only related to capsular and ligamentous tightness but also fascial restrictions, muscular tightness, and trigger points within the muscles.

Acupuncture points SI10, LU1, GB21, SI11, SI12, HT1, and Ex-HN15 are recommended for the treatment of shoulder pain. Usually 1 mL of placental extract is injected to each acupuncture point, while a 40–60-mm-long 23 gauge needle is inserted to a depth of 25–40 mm. SI10 (**Figure 3A**) is localized on the posterior scapulohumeral joint, while LU1 (**Figure 3B**) is localized at the medial margin of coracoid process. In order to successfully infuse placental extract into the anterior scapulohumeral joint, the tip of needle should be entered LU1 and proceeded toward the anterior scapulohumeral joint.

SI11 (**Figure 3A**) is localized on the upper third of the line connecting the midpoint of the spine of scapula and the lower margin of scapula [60] and coincides with the trigger point of infraspinatus muscle. SI12 (**Figure 3A**) is located in the scapular region, in the supraspinatus fossa, superior to the midpoint of the spine of the scapula [60]. Clinically meaningful improvements were reported in pain and disability, while trigger points of upper trapezius, supraspinatus, and infraspinatus musculature were intervened by needling [69]. As SI11, SI12, and GB21 (**Figure 3A**) coincide with the trigger points of the infraspinatus, supraspinatus, and

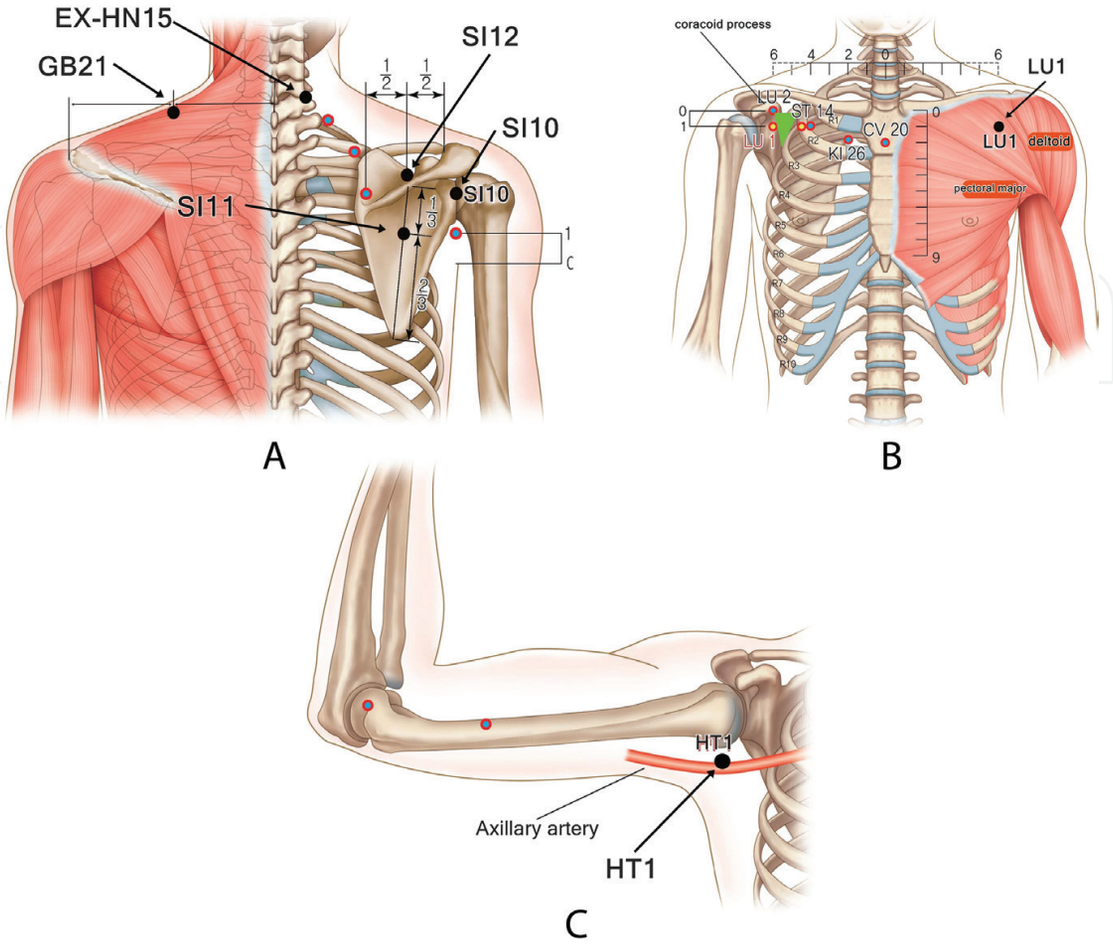


Figure 3. Acupuncture points for treating shoulder pain.

trapezius, respectively, injections of placental extract to SI11, SI12, and GB21 relieve tightness or pain in these muscles which are associated with range of motion limitation in neck and shoulder joints. Through HT1 (**Figure 3C**) on axillary fossa, the tip of needle can be finally placed on subscapularis muscle, which plays a key role in the development of adhesive capsulitis [70]. Ex-HN15 (**Figure 3A**), a member of extra channel acupuncture points, is selected for spinal modulation of shoulder joint innervation.

6.3. Knee arthritis

Arthritis means inflammation of the joints. The symptoms of knee arthritis are intermittent pain, swelling, redness, and stiffness in the joints. There are many different types of knee arthritis; some of which are rheumatoid arthritis (RA), osteoarthritis (OA), and infectious arthritis. In RA, the joints are destroyed by the immune system. OA pain is due to inflammation, which may be present in bone tissues, cartilages, joints, disks, ligaments, soft tissues, and muscles. OA affects not only the articular cartilage but also the underlying bone and adjacent joint structures. Inflammation of the synovial membrane may be absent in the earlier stages of OA. However, as the disease progresses, some degree of synovitis usually exists in OA [71].

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IL-1, a cytokine produced by chondrocytes and other cells in the joint, plays an important role in cartilage degradation in OA by stimulating the synthesis of degradative enzymes that inhibit the production of proteoglycan [72]. Other cytokines that appear to act synergistically with IL-1 to promote matrix breakdown in OA are TNF-α and IL-6 [73].

Knee OA is a chronic progressive disease affecting more than 20% of people older than 45 years [74]. With the increase in life expectancy, it seems that the need for knee arthroplasty would rise, causing significant economic burdens for pain control and rehabilitation of patients. The target of knee OA treatment is pain decrement, function and mobility increment, prevention or correction of the deformity, and slowing the progression of the disease.

In regarding pain control and movement rehabilitation, acupuncture points ST35 can be chosen for API with placental extract. At the same time, APIs with placental extract to KI10, SP10, GB34, GB31, and BL25 are also helpful to ameliorate the symptoms of knee OA. ST35 (**Figure 4A**) is localized on the lateral margin of patella tendon along the knee joint line [60]. Through ST35, 6–8 mL of placental extract is reached in the synovial joint cavity by using a 10-mL syringe with 40-mm-long 23 gauge needle.

Acupuncture point SP10 (**Figure 4A**) is localized on the belly of vastus medialis muscle, GB31 (**Figure 4B**) is on vastus lateralis muscle, and GB 34 (**Figure 4C**) is on the head of fibula in the region of lower extremity. These three acupuncture points concord to the trigger points of the vastus medialis, vastus lateralis, and fibularis muscles, respectively. Acupuncture point KI10 (**Figure 4D**) is located between the tendons of semitendinous and semimembranous muscles in the region of popliteal fossa [60]. From our clinical experience, it is proposed that treating muscles around the knee joint is indispensable to improve stability of knee joint. Using a sterile syringe with 40-mm-long 25 gauge needle, each 1 mL of placental extract is injected to KI10, SP10, GB31, and GB34. BL25 (**Figure 4E**) is localized on the facet joints of L4 and lies on the paravertebral muscles including longissimus, rotator, and multifidus. For the injection to BL25, the entering point of the needle is 2.5 cm lateral from the median line, with a needle depth of 2.5–4 cm. A total of 1 mL of placental extract is injected to BL25 by a 3-mL syringe with 60-mm-long 25 gauge needle.

6.4. Fibromyalgia syndrome

Fibromyalgia syndrome (FMS) is a chronic, painful musculoskeletal disorder characterized by widespread pain, pressure hyperalgesia, morning stiffness, sleep disturbances, fatigue, and physical and psychological distress [75]. It can be divided into two forms: the primary form, with very pronounced psychogenic background, and the secondary form with rheumatic arthritis, systemic lupus erythematosus, Sjögren syndrome, or inflammatory bowel disease. Fibromyalgia has been proposed to be due to neurogenic inflammation induced by an inflammatory response to allergen, infectious agents, irritants, chemical exposures, or emotional stress [76]. Several studies have shown that there are increased levels of inflammatory neurotransmitter substance P and calcitonin gene–related peptide (CGRP) in the spinal fluid of patients with FMS [77]. Another study found increase in blood levels of cytokines IL-6 and IL-8, whose release is stimulated by substance P [78].

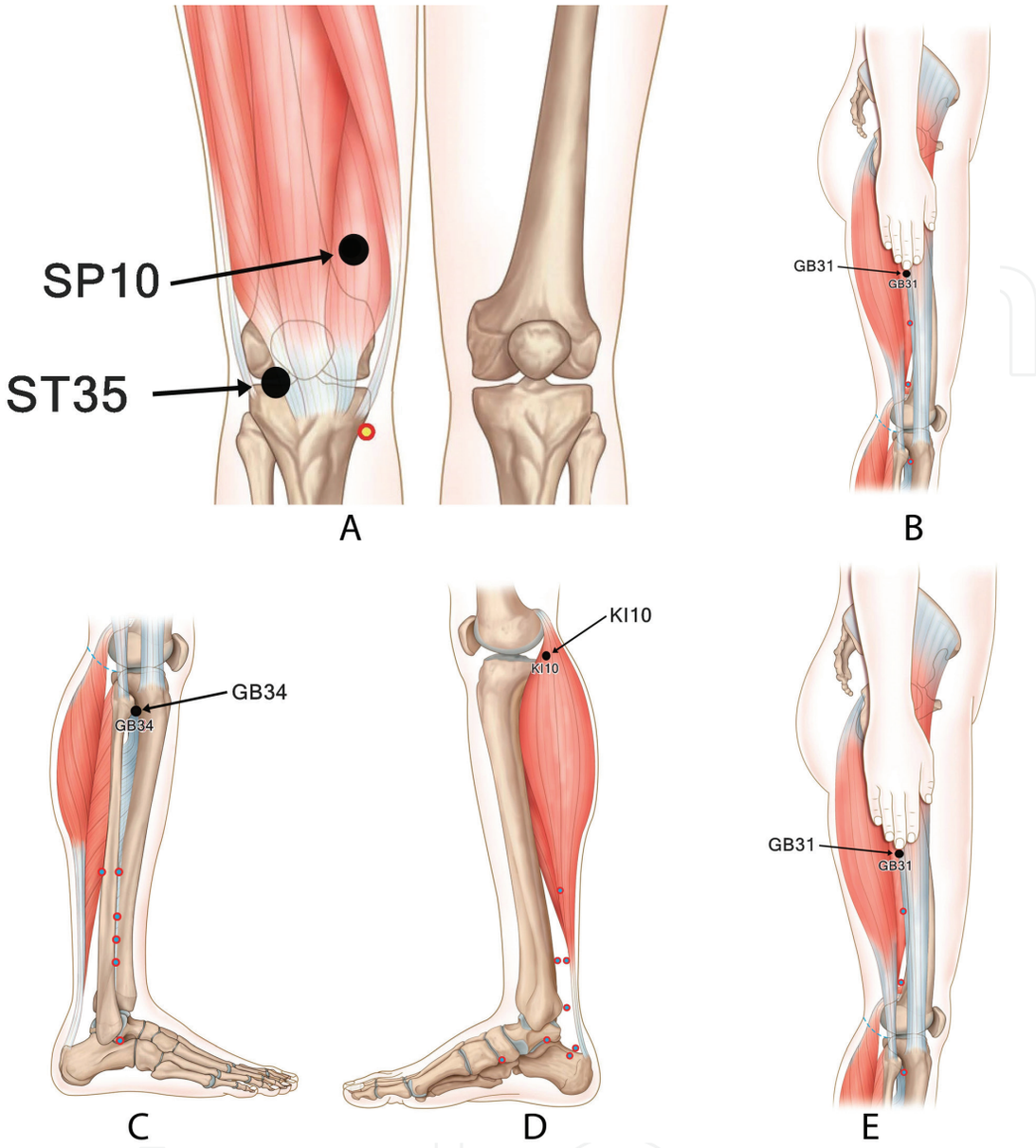


Figure 4. Acupuncture points for treating knee arthritis.

Various forms of physical trauma have been implicated as triggering events in the pathogenesis of FMS, and some patients report the initiation or exacerbation of their symptoms after a traumatic event such as a whiplash injury [79]. It was estimated that between 2.9 and 3.8% of the general population in Europe and the US are affected [80], and the majority of patients in clinical setting belongs to female. The polysymptomatic distress score (PDS) can be used to diagnose FMS. It is derived from a compilation of the number of pre-specified painful regions, which a patient has plus a rating of the severity of pain, sleep disturbance, fatigue and cognitive dysfunction, headache, abdominal pain, and depression [81]. Although there is no satisfactory treatment for FMS as yet, many patients with FMS utilize complementary and alternative medicine (CAM) therapies in addition to conventional medicine. Acupuncture is one of the most commonly employed CAM therapies.

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The recommended acupuncture points for the treatment of FMS are GB21, SI11, SI13, SI14, Ex-HN15, and BL13 (**Figure 5**). SI13 is located on the medial margin of the spine of scapula and coincides with the trigger point of supraspinatus muscle. As women with FMS show higher pain sensitivity and lower pressure pain thresholds over cervical spine and supraspinatus [82], choice of SI13 is pertinent. BL13 is located 2.5 cm lateral from the bottom of the spinous process of T3 [60] and corresponds to the trigger point of the upper rhomboid major muscle. According to the outcome of cervical pathology study, myofascial trigger points are commonly observed in the neck, parascapular region, and upper back muscles [83]. Therefore, API with placental extract to GB21, SI11, SI13, SI14, Ex-HN15, and BL13 can be used to improve the symptoms of FMS by relieving complications derived from the pathological condition of neck. A sterile 40-mm-long 23 gauge needle is inserted into the acupuncture points as patients are seated. Usually, each 1 mL of placental extract is injected to the acupuncture points, while needles are inserted to a depth of 25 mm.

6.5. Complex regional pain syndrome

Complex regional pain syndrome (CRPS) is often initiated by trauma to a nerve, neuronal plexus, or soft tissue. Diagnostic criteria are the presence of regional pain and other sensory changes following painful injury. The pain is associated with changes in skin color, skin temperature, abnormal sweating, and tissue swelling. With time, tissue atrophy may occur as well as involuntary movements, muscle spasm, or pseudoparalysis. The inflammatory mediators that are generated, especially IL-6, accelerate the rate at which bone is broken down [84].

At the start, soft tissue or nerve injury causes release of inflammatory mediators and excitation of sensory nerve fibers. Reverse firing of sensory nerves causes release of the inflammatory neuropeptides such as substance P, CGRP, and amino acids such as glutamate at the peripheral

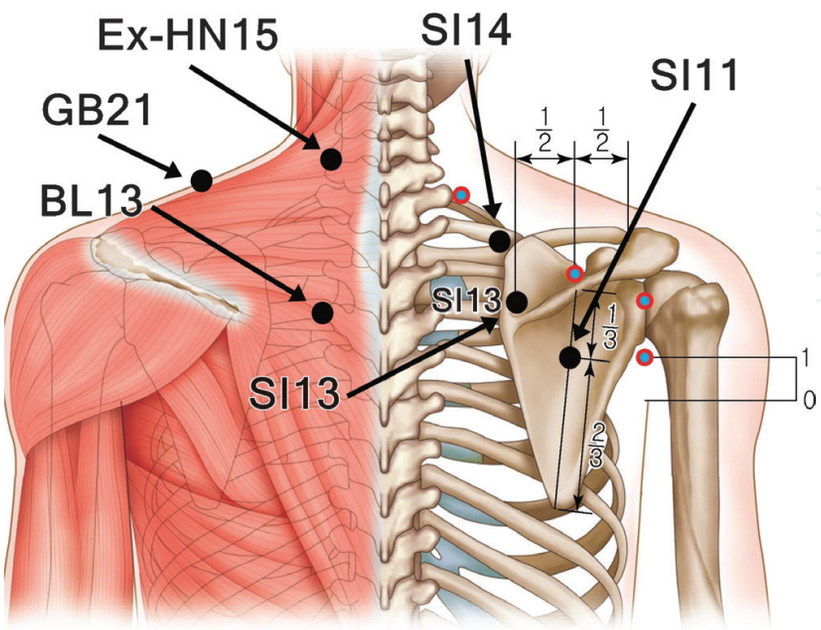


Figure 5. Acupuncture points for treating fibromyalgia.

endings of sensory fibers. These neuropeptides may induce vasodilation, increase vascular permeability, attract other immune cells, and excite surrounding nerve fibers. At the level of central nervous system, the increased input from peripheral pain receptors alters the central processing mechanisms. Perpetuation of the sympathetic response has been proposed to be related to central dysregulation of nociceptive impulses. Prolonged ischemia from sympathetic

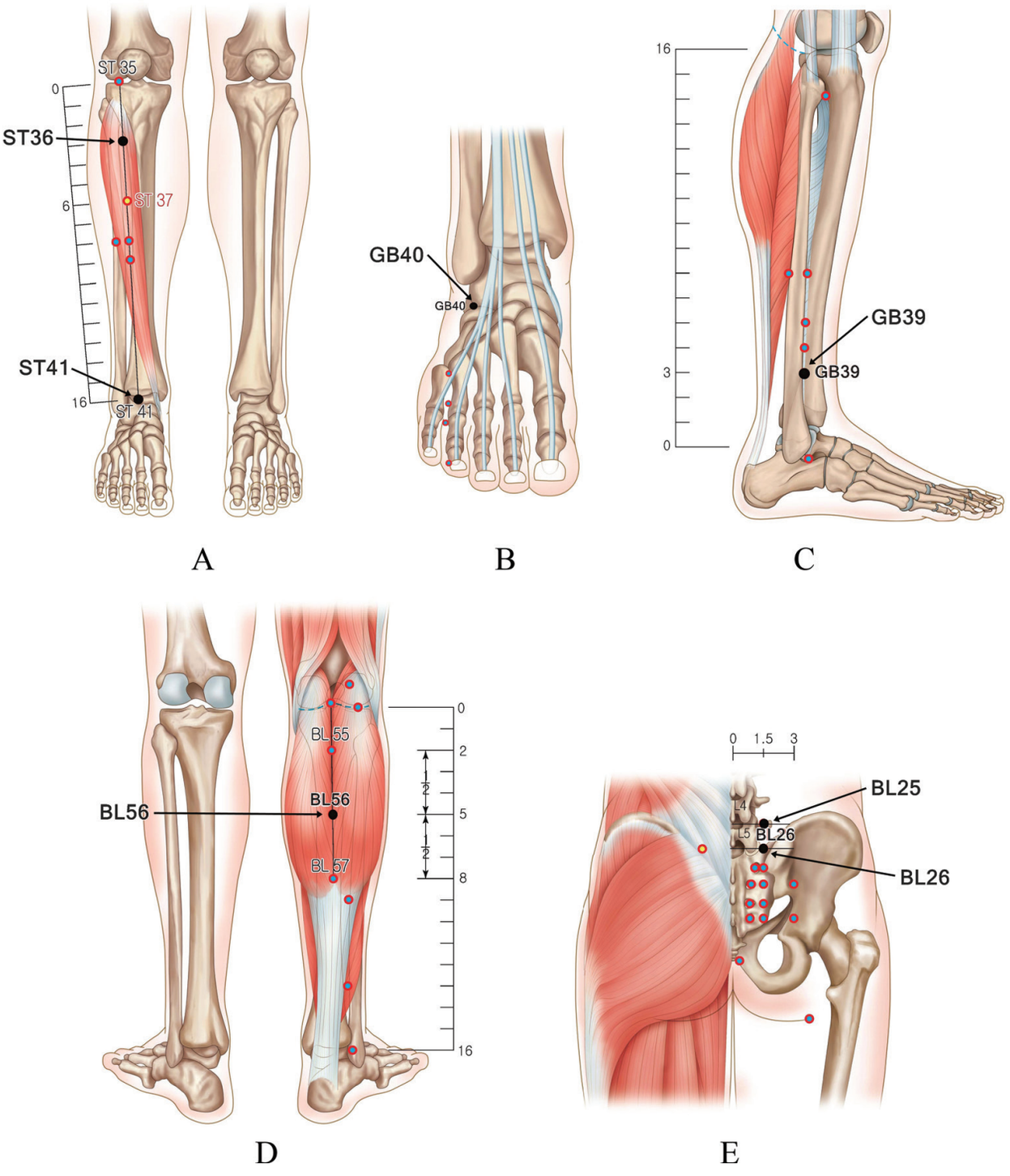


Figure 6. Acupuncture points for treating complex regional pain syndrome.

http://dx.doi.org/10.5772/intechopen.79718

vasoconstriction produces more pain, establishing a reflex arc that promotes further sympathetic discharge and vasospasm. The results of several experimental studies suggest that sympathetic dysfunction may also consist of super sensitivity to catecholamines induced by nerve injury [85]. In the final, CRPS exhibits allodynia where otherwise innocuous stimulation will cause pain and hyperalgesia where there is exaggerated pain to a known painful stimulus. Regional osteopenia, changes of hair and nail growth, and dystrophic cutaneous changes may also occur. The magnitude of each of these features will vary between individuals, each existing on a wide spectrum. Usually, patients with CRPS affecting wrist/hand regions have neck and shoulder girdle signs on the affected side, while patients affected with ankle/foot regions suffer from back pain and lower extremity dysfunction on the affected side.

The recommended acupuncture points for the treatment of CRPS affecting ankle/foot regions are ST41, GB40, GB39, BL56, ST36, BL25, and BL26. ST41 (**Figure 6A**) is located on the anterior aspect of the ankle, in the depression at the center of the front surface of the ankle joint, between the tendons of extensor hallucis longus and extensor digitorum longus [60]. GB40 (**Figure 6B**) is located in the depression lateral to the extensor digitorum longus tendon, anterior and distal to the lateral malleolus [60]. Through ST41 and GB40, each 1 mL of placental extract is infused to the ankle joint using a 3-mL syringe with 30-mm-long 23 gauge needle.

To rehabilitate the ankle joint, GB39 (**Figure 6C**), BL56 (**Figure 6D**), and ST36 (**Figure 6A**) are suitable to be administered with placental extract. Injection to GB39, BL56, and ST36 contributes to the mediolateral stability of the ankle joint complex (i.e., talocrural and subtalar joints) by relieving the muscle tension. Each 0.5 mL of placental extract is injected to GB39, BL56, and ST36 with 40-mm-long 25 gauge needles. BL25 and BL26 (**Figure 6E**) are located at the same levels as the inferior border of the spinous process of L4 and L5, respectively. They are situated 2.5 cm lateral to the posterior median line. There is compelling evidence that lower extremity arthrosis is related with lumbar spinal disease [86]. Using 710 randomly selected cadaveric specimens, a significant association was found between lumbar disk degeneration and tibiotalar joint arthritis [87]. A cross section study comparing normal subjects and patients with lumbar disk herniation with sciatica revealed that ankle plantar flexion torque was significantly lower in the lumbar disk herniation group than the control group [88]. Moreover, in a preliminary study with collegiate football players, low back dysfunction and suboptimal endurance of the core musculature appear to be important injury risk factors for strains and sprains of foot [89]. Each 1 mL of placental extract is injected to BL25 and BL26 by 3-mL syringes with 60-mm-long 25 gauge needle.

7. Conclusion

Acupuncture point injection (API) is one of effective therapeutic interventions on inflammation-involving pain diseases, which are caused by structural injury or functional degeneration. The origin of all pain is inflammation and the inflammatory response. API with placental extract provides therapeutic effects by anti-inflammatory and regenerative effects on injured or degenerative tissues. We describe treatment methodology of API with placental extract in pain syndromes focusing on pain relief and joint mobilization. The loci of acupuncture

points adopted in API with placental extract are the joints, muscles responsible for the movement of the joints, and the paravertebral muscles regulating the innervation of the joints.

Acknowledgements

We appreciate Dr. Cheol O Joe, Korea Advanced Institute of Science and Technology for comments on this manuscript.

Conflict of interests

Authors disclose no potential conflicts of interest.

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