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Mechanism and Research Progress of Acupoint Injection in the Treatment of FS

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Abstract. Frozen Shoulder (FS), as a common shoulder joint disorder, faces dual challenges of pain control and functional recovery in clinical treatment. This paper systematically reviews the action mechanism and clinical research progress of acupoint injection therapy for FS. Grounded in the meridian-acupoint theory of traditional Chinese medicine and modern pharmacological studies, acupoint injection combined with other therapies exerts effects of inhibiting inflammatory factors and fibrosis, regulating bone metabolism and nerve function, and improves the living status of FS patients. Supported by modern technologies, ultrasound guidance and transmission electron microscopy enable more precise research and clinical application of acupoint injection. However, current studies still have limitations such as insufficient standardization of acupoint selection and unclear mechanism of drug compatibility. Future work should deepen mechanism exploration through multicenter trials and animal models to promote the development of acupoint injection therapy.

Keywords: FS, acupoint injection, mechanism

1. Introduction

Frozen Shoulder (FS) belongs to the category of "arthralgia syndrome" in traditional Chinese medicine. *Acupuncture and Moxibustion for Health Preservation* put forward the first disease name with connotation similar to that of modern periarthritis of shoulder [1]. The core pathogenesis of this disease is meridian obstruction and qi-blood stasis. Modern medicine holds that it is associated with chronic inflammation and adhesion of the shoulder joint. Conventional treatments yield unsatisfactory effects, while acupoint injection features the advantages of "synergistic effect of acupuncture and medicine, precise targeting" [2]. It can also reduce drug side effects, improve therapeutic efficacy, and boasts simple operation and low cost. As an administration route, it represents an innovation in the integration of traditional Chinese and Western medicine. Multiple studies have demonstrated that this therapy achieves better efficacy than single acupuncture or single drug administration. Combined with recent articles on acupoint injection for frozen shoulder, this paper summarizes its mechanism and research progress.

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2. Mechanism of acupoint injection in the treatment of FS

Acupoint injection exerts therapeutic effects through meridian-acupoint stimulation, drug action, and the interaction between drugs and acupoints, which elevates local drug concentration and regulates the neuro-humoral-immune network. Studies on the pathogenesis of periarthritis of shoulder indicate that multiple substances participate in the development of FS, including inflammatory mediators cyclooxygenase (COX-1, 2), interleukin (IL-1, 6), tumor necrosis factor (TNF-α), insulin-like growth factor IGF-2, acid-sensing ion channel ASIC, transforming growth factor TGF-β and other cytokines. The mechanical stimulation of acupoints and chemical stimulation of drugs work together to produce therapeutic effects.

2.1. Theoretical basis of acupoint injection

Acupoint injection has targeted regulation capacity, delivering drugs to the lesion site via meridians. Meanwhile, acupoint stimulation enhances efficacy and strengthens qi-blood circulation and nourishment.

2.1.1. Synergistic effect of meridians and acupoints

In acupoint injection therapy, the main components of traditional Chinese medicine injections mostly act directly on shoulder acupoints, which falls into local meridian guidance in the meridian tropism theory [3]. This endows drugs with selective distribution in the body and produces rapid and potent pharmacological effects, a phenomenon known as drug-acupoint tropism [4]. According to the meridian theory of traditional Chinese medicine, multiple meridians traverse the shoulder. Through acupoint injection, the action information of drugs on the shoulder may be transmitted to periacromial tissue cells in the form of non-specific signals via cell junction communication in the meridian structural system, and then converted into specific physiological responses through intracellular messenger cascade [5]. Current studies have proposed various theories on the nature of meridians, including the porous medium channel theory dominated by continuous liquid phase, the semiconductor-like property of acupoints, and the trace element theory [6, 7]. Modern research shows that stimulating acupoints near the lesion can improve microcirculation, increase local blood flow, activate mitochondria and accelerate the repair of skeletal muscle injury [8].

2.1.2. Synergistic effect of injections

Traditional Chinese medicine injections most likely exert the physiological effects of active ingredients through local action and intracellular signal transduction. Common preparations such as Angelica sinensis injection, Zhengqing Fengtongning injection, Shenmai injection and Danchuan injection [9] are mostly derived from herbs with the function of activating blood circulation and dredging collaterals. These injections exert therapeutic effects by promoting the absorption of inflammatory substances, nourishing nerves [9], regulating calcium and phosphorus metabolism [10, 11], and improving microcirculation, with the advantage of mild side effects.

Western medicine injections also deliver favorable effects in acupoint injection. Commonly used agents include anesthetics, neurotrophic drugs and anti-inflammatory drugs, such as cobamamide, caine derivatives, triamcinolone acetonide and corticosteroids. These drugs have the effects of inhibiting inflammatory factors, suppressing fibrosis and repairing nerves.

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2.2. Action mechanisms of acupoint injection

The definition of FS has been clearly specified in orthopedics and traumatology guidelines: FS refers to a disease characterized by shoulder pain and motor dysfunction caused by lesions of periacromial soft tissues (periacromial muscles, tendons, bursae and joint capsule), also known as frozen shoulder or adhesive arthritis [12]. Based on its pathogenesis and common acupoint injection regimens, the mechanisms can be categorized into inhibition of inflammatory factors, suppression of fibrosis, regulation of bone metabolism, and nerve nourishment and repair.

2.2.1. Inhibition of inflammatory factors

The inflammatory response in the early stage of frozen shoulder (FS) is associated with fibroblast recruitment. Studies have confirmed chronic inflammatory cell infiltration in rotator interval biopsies of FS patients. Some scholars measured the levels of inflammatory cytokines in the subacromial bursa of frozen shoulder patients and found significantly elevated expression of IL-1α, IL-1β, TNF-α, COX-1 and COX-2. These changes may be related to the progression from inflammation to fibrosis, and also indicate that various inflammatory factors play important roles in joint pain and limited mobility in FS. Common traditional Chinese and Western medicine acupoint injections promote histamine release, induce the secretion of T lymphocytes and anti-inflammatory factors, and exert anti-inflammatory and anti-fibrotic effects [13].

2.2.2. Suppression of fibrosis

The synovial fluid of FS patients contains substances that promote fibroblast proliferation. Fibrosis occurs in the extracellular matrix (ECM) of periacromial inflammatory tissue due to dysregulation of enzymes such as MMP, and fibroblast proliferation can be detected in biopsy samples. Immunohistochemical analysis of FS tissues by Rui Yang et al. showed that compared with the control group, the expression of ECM markers such as type I collagen, type III collagen and fibronectin was significantly increased in frozen shoulder tissues. P65 (NF-κBp65) plays a key role in FS fibrosis by promoting the expression of fibrosis-related factors such as TGF-β. Acupoint injection agents such as ozone water can effectively reduce its mRNA and related protein expression. Studies by Tian Mingyue et al. found that acupoint injection of ozone water significantly downregulated the mRNA and protein expression of P65 and IKKβ in mouse cartilage tissue [12, 14].

2.2.3. Regulation of bone metabolism

Bone metabolism disorder is one of the factors inducing and aggravating FS. 25-hydroxyvitamin D3 is the gold standard for evaluating the vitamin D status of the body [15]; N-terminal osteocalcin, type I procollagen amino-terminal propeptide and β-crosslaps are common clinical bone metabolism markers. Acupoint injection can affect bone metabolism and vitamin D levels through specific acupuncture effects. Multiple studies have found that acupoint injection increases BMD [16], raises bone mineral and bone collagen content, and enhances bone strength. Acupoint injection can also generate bioelectrical activity, participate in the regulation of the HPA axis [17], and inhibit the progression of bone destruction [18].

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2.2.4. Nerve nourishment and repair

Studies have shown that around the joint capsule of frozen shoulder, cytokines and immune factors related to pain and fibrosis are distributed along with increased neovascularization and regenerated nerve fibers [19]. The inflammatory microenvironment may activate apoptosis, ferroptosis and other processes, leading to nerve injury around the shoulder joint and consequent pain. Lidocaine exerts ion channel blockade on motor and sensory nerve functions in FS treatment; it may reduce neuronal apoptosis and inflammatory response by activating the Notch signaling pathway [20], thereby alleviating local periacromial injury. Cobamamide, one of the active coenzyme forms of vitamin B12 and an essential coenzyme for nucleotide synthesis, is also commonly used in FS treatment [21]. It can reduce the overexpression of hypoxia-induced apoptotic protein Caspase-3 and inhibit neuronal apoptosis [22]. Meanwhile, it promotes the production of lipoprotein in the nerve myelin sheath, maintains myelin integrity, and plays a critical role in cell growth, proliferation and metabolism [23].

3. Acupoint selection schemes for acupoint injection in FS treatment

Acupoint selection generally follows the principle of "local acupoints as the mainstay, distal acupoints as the supplement" [24]. Common injection sites include various meridian acupoint combinations such as the "three shoulder acupoints", local Ashi points, trigger points, meridian sinew knot points and specific points. The location of Ashi points on the shoulder varies among FS patients. Trigger points refer to myofascial trigger points, which are tender spots on skeletal muscle that can induce pain [25]. *Chinese Meridian Sinew Science* states that palpation along the affected upper limb and shoulder joint identifies meridian sinew knot points when obvious tenderness accompanied by cord-like induration or local tissue swelling and thickening is detected [26]. Injecting medication at the knot point can rapidly relieve local symptoms, achieving the effect of "both acupuncture and medicine reaching the lesion" [27, 28]. Besides proximal acupoint selection, distal acupoints such as Zusanli, Quchi, Waiguan and Yanglingquan [29] are also used as adjuvant points in clinical practice. Distal acupoint selection is based on the principles of "where the meridian passes, its indications cover" and "like attracts like", as well as the therapeutic rules of "drawing yang from yin, drawing yin from yang, treating the left side by the right, and treating the right side by the left", embodying the ancient Chinese philosophical concept of "harmony" [30].

4. Technological innovation and efficacy optimization of acupoint injection

4.1. Enhanced efficacy via combined acupoint injection regimens

Acupoint injection is usually applied as part of combination therapy alongside other clinical treatments for different types of FS patients. Clinical regimens can combine shock wave therapy, round-sharp needle, exercise therapy, small needle scalpel, tuina manipulation and other methods [2, 9, 10, 31]. Compared with acupoint injection alone, combined therapy results in lower VAS pain scores and improved shoulder range of motion, with superior efficacy to monotherapy. Combined treatment has basically become a clinical consensus for frozen shoulder. Acupoint injection is not only used for FS but also widely applied to various other diseases such as chronic pain, osseous diseases [11], rheumatic diseases [32] and neuropathic pain disorders [33], all with favorable therapeutic effects.

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4.2. Improved accuracy via acupoint injection combined with modern medical positioning technology

During acupoint injection treatment, internal structures cannot be directly visualized, and improper operation may easily cause injury. Modern science and technology have effectively addressed this issue. Furthermore, modern technologies enable microscopic research on shoulder tissue changes in FS patients. Lü Hongmei et al. used modern ultrasound technology to perform trigger point acupoint injection of mecobalamin and triamcinolone acetonide for FS, and adopted the Mindray M7 ultrasound system for shoulder joint examination in another experiment [13, 25]. Ultrasound allows comprehensive observation of soft tissue structural relations in a non-invasive manner, facilitating accurate assessment of physiological and pathological morphological and structural changes of soft tissues. Modern transmission electron microscopy enables clear observation of the effects of acupoint injection on nerve tissue. Peng Weijie et al. employed this technique to investigate the impacts of drug compatibility and injection sites on nerve injury in rats [34]. Currently, nanotechnology exerts a profound influence on medicine with its advantages of small size and enhanced therapeutic effect, and has been applied in fields such as nano-acupuncture and nano-drug delivery systems. In the future, the combination of nanomaterials and acupoint injection may be utilized to study a series of changes in shoulder tissues, and even improve needle devices to reduce injection wounds [35-37].

5. Deficiencies and prospects

In recent years, acupoint injection for FS has developed rapidly, with a growing number of relevant literature reports and accumulated extensive clinical experience, and its therapeutic efficacy is well recognized. However, from a clinical perspective, there are still issues such as non-standard and inaccurate operation, drug compatibility and dosage [6], and cases of peripheral nerve injury caused by acupoint injection have been reported. From the perspective of experimental research, there is a lack of experimental studies on the mechanism of acupoint injection for FS. First, the level of evidence is relatively low. Meta-analysis by Liu Huan et al. shows that there is currently a shortage of multicenter, large-sample randomized controlled trials, and most studies have short follow-up periods without long-term observation [38]. Second, acupoint selection is relatively monotonous, focusing mainly on local points, with insufficient research on optimal acupuncture prescriptions for different disease stages. Third, drug selection lacks uniformity and innovation. Some drugs used for acupoint injection still cause adverse reactions, and few studies have revealed the underlying mechanisms; although scholars have verified the feasibility of using TET to inhibit the onset and progression of frozen shoulder, relevant research remains at the animal experiment stage. Fourth, most evaluation indicators in clinical studies of acupoint injection are subjective, lacking objective data support.

This paper proposes that novel needle devices can be improved to leverage the advantages of acupuncture techniques, and enhanced acupuncture stimulation can further boost therapeutic efficacy. There are diverse combinations of the three shoulder acupoints, and different needling techniques such as three-shoulder penetration needling and golden-hook fishing needling also produce different effects [39]. In the future, we should give full play to the strengths of traditional Chinese medicine theory, study the holistic effects of acupoint injection, continuously summarize the advantages of various combined acupoint injection regimens, explore methods to effectively shorten the treatment cycle, and provide new ideas for clinical practice. Systematic and standardized experimental designs should be carried out to conduct histomorphological observation and

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pathological research on drug types and compatibility, injection dosage and concentration, injection depth, medication frequency and time interval in acupoint injection, so as to clarify the impacts of various factors on local muscles, blood vessels and nerves. On this basis, the regimen with the least adverse effects can be screened as a routine clinical protocol, providing experimental evidence for rational clinical drug selection and medication frequency [40].

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