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Review Article

Is there a role of ultrasound stimulation in pain management? A literature review

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Abstract: Short pulse of focused ultrasound can stimulate the receptor structures of human tissues in particular pain sensations. It can be widely used to promote recovery after nerve and tendon injuries, stroke hemiplegia, herpes zoster, acute mastitis, chronic pelvic pain. In this paper, we provide a brief review on the applications of sonophoresis, especially on pain management, mechanisms of sonophoresis, animal experiments and the problems of sonophoresis. This paper may provide a reference for further applying ultrasound stimulation to disease treatment.

Keywords: Ultrasound, sonophoresis, cavitation, pain management

Introduction

Pain sensations from nerve and tendon injuries are usually chronic. The recovery and control of chronic pain are the primary problems that need to be resolved. Low-intensity ultrasound stimulation is a non-invasive and topical method for therapeutic strategies. It represents a considerable technology compared to traditional surgery or oral drug delivery. As chronic nerve and tendon injuries can set off inflammation and scar formation, impact the function of joints, this is not indication of surgery, and first-pass metabolism through the liver cannot be avoided for oral drugs delivery [1], and this will have less impact than we might expect. Both of them are not ideal methods for treating chronic nerve and tendon injuries.

Ultrasound stimulation is an effective method for pain management. Short pulse of focused ultrasound is the low-intensity ultrasonic wave that has been used for soft tissue healing [2] and enhancing the drug delivery across the skin [3]. This type of enhancement is indicating the therapy period depends on the influence of ultrasonic energy. Sonophoresis is firstly reported in the 1950s along with other therapeutic ultrasound applications such as noninvasive treatment of neurological disorders [4]. From previous studies [5-7], the therapeutic intensity is 0.5-2.5 w/cm^2. The low-intensity ultrasound has been applied to stimulation and increasing skin permeability of various drugs. In this paper, we provide a brief review on the application of US, its mechanisms and its role on pain management.

Applications of sonophoresis

The applications of ultrasound stimulation include pain management in nerve and tendon injuries, stroke hemiplegia, herpes zoster, acute mastitis, and chronic pelvic pain. Since the initial treatment of polyarthritis with hydrocortisone ointment, the sonophoresis in transdermal delivery of therapeutic drugs such as fentanyl, caffeine, heparin, ketoprofen and insulin has become a major concern for clinical medicine [4].

Sonophoresis in nerve and tendon injuries

Chronic pain from osteoarticular injuries is a common condition including cervical spondylosis, periarthritis of shoulder, arthritis of the knee, tennis elbow, chronic Achilles tendon pain, carpal tunnel syndrome. As arthritis of knee and carpal tunnel syndrome for examples, ligaments of the knee are easy to injury in

sports or traffic trauma. The joint becomes swelling and painful, and are difficult to walk. Chronic injuries will set off scar formation, and impact the function of joint. Carpal tunnel syndrome (CTS) is a neurologic disorder involving compression of median nerve in the carpal tunnel of wrist [8, 9]. It leads to impaired nerve conduction and nerve dysfunction [8]. The symptoms of CTS include sensory impairments such as tingling, numbness, pain of hand and motor impairments such as thenar muscle weakness, hand dexterity and function loss [10]. CTS is an unpredictable course, and is potentially a difficult condition to treat [11].

Ultrasound stimulation is a considerable treatment for chronic pain from soft tissue and nerve injuries. This therapeutic method adopts low-intensity ultrasonic wave alternated exposure. The effects of ultrasound stimulation on nerve and tendon injuries are speculatively the best, and the alteration in function is due to the effect of ultrasound stimulation on transport across cell membranes and on enhancement of circulation. The application of low-intensity ultrasound stimulation after peripheral nerve crush or transection and repair will be an interesting area of exploration [12]. The mechanisms depend on mechanical and thermal effects. It can provide anti-inflammatory, cell-repair and pain-control functions, which will be discussed in section three.

Sonophoresis in stroke hemiplegia

The chronic back pain or affected part pain usually happen after stroke hemiplegia. The stroke hemiplegia impacts the nerve, leading to vasospasm, swelling and pain. Due to pain, the functions of limbs are limited. This is a difficult problem and it is hard to be adequately resolved by surgery or oral drugs delivery. The function recovery is the primary solution. Sonophoresis produces the sound wave which was transmitted to the affected area through a handheld probe using conductive gel, can penetrate the deep tissues and improve the healing [13]. Low-intensity ultrasound is placed on the affected area to provide the heat. It can promote the muscle relaxation through vasodilatation and decrease the inflammation. In addition, it decreases the nerve conduction, increases the pain threshold, and supports obvious analgesic effect. The mechanisms of thermal effect will also be discussed in section three.

Sonophoresis in herpes zoster

Herpes zoster is caused by varicella zoster virus. The symptoms are skin pain and herpes. The pain emerges frequently through peripheral nerve supply. The quality of life is impacted by chronic nerve pain, and it is hard to treat by surgery or drugs. The applications of ultrasound stimulation to enhancing recovery in peripheral nerve pain: including reducing pain and improving function with entrapment neuropathies and facilitating the regeneration [12]. A large variety of nonsurgical therapeutic methods have been attempted to resolve symptoms from herpes zoster. Patients were treated with pulsed ultrasound stimulation at 1.0 w/cm^2 (5 min daily for two weeks) [14] have greater relief of symptoms and greater improvement in peripheral nerve conduction velocity.

Sonophoresis in acute mastitis and chronic pelvic pain

Acute mastitis often occurs in lactating women. It is caused by galactostasis in the breast which leads to bacterial reproduction and abscess. In acute mastitis, the breast becomes red, warm and pain. The chronic pelvic pain is also a common gynecological disease, of which the reasons include chronic pelvic inflammation, endometriosis, pelvic adhesion and pelvic venous stasis. It is difficult to get effective solution for these two kinds of disease, and the nonsurgical methods are considered firstly. Low-intensity ultrasound stimulation can be used to treat the acute mastitis and chronic pelvic pain. This delivery method uses pulsed ultrasound stimulation wave (0.6-0.8 w/cm^2) to produce heating and vasodilatation effect [7]. For chronic pelvic pain, 1.0 w/cm^2 ultrasound stimulation is used, and the sonophoresis in transdermal delivery of therapeutic drugs can enhance the drugs penetration in deep tissues and organs, and improve the therapeutic effects [15].

Sonophoresis in transdermal drug delivery

US can combine with transdermal drug delivery for the enhanced treatment. The drugs include Chinese traditional medicine, voltaren and others drugs such as fentanyl, caffeine, heparin, ketoprofen and insulin. Borcaud et al [16] have evaluated the effects of sonophoresis (20 kHz, 2.5 w/cm^2) on transdermal transport of fentanyl and caffeine across human skin, and ob-

tained good outcomes. Fentanyl is generally used to relieve pain in surgery or cancer patients, while caffeine is the most common stimulant used for treatment of lipodystrophy [17]. Above results show that, sonophoresis can enhance the transdermal drug delivery. Mitragotri et al [18] have performed in vitro experiments with sonophoresis (20 kHz, 7 w/cm^2) to deliver heparin or low-molecular weight heparin across the skin. Results find that, patients can use drug based on this technology throughout the whole day to provide sustained heparin concentration in the blood. The dose of heparin can be controlled through skin permeability and treatment area in the reservoir of the patch system under the effects of sonophoresis. Ketoprofen is a non-steroidal anti-inflammatory drug predominantly used for treatment of rheumatoid arthritis and osteoarthritis and relieve minor aches and menstrual pain [19, 20]. Herwadkar et al [21] have tested the effects of sonophoresis (20 kHz, 6.9 w/cm^2) for delivery of ketoprofen across the skin. The results show that, sonophoresis with frequency of 20 kHz is an effective technique to improve the transdermal and topical delivery of ketoprofen.

Among the transdermal drug delivery techniques, the noninvasive transdermal delivery of insulin has received great attention due to the increased incidence of diabetes, one of the most costly diseases in all patient populations and age groups [22]. Management of diabetes often requires painful and repetitive insulin injections up to three or four times daily [23]. Non-invasive insulin delivery through the skin may be a preferable technique for diabetic patients. Numerous studies [22, 24, 25] have been performed on the transdermal insulin delivery. Smith et al [25] have evaluated the feasibility of sonophoresis in insulin delivery to enhance the in vitro transport of insulin across human skin. The results show that, the ultrasound stimulation on transdermal drug delivery mode can relieve the chronic pain.

Mechanisms of sonophoresis

Although sonophoresis is known to enhance the pain management by low-intensity ultrasonic wave stimulation and skin permeability, the fundamental mechanism is still not characterized. Several proposed mechanisms of sonophoresis include mechanical and thermal effects by absorption of ultrasound energy, and cavitation effects caused by collapse and oscillation of cavitation bubbles [4]. Cavitation is believed to be the predominant mechanism responsible for sonophoresis on transdermal drug delivery [26-28].

Mechanics effect

Ultrasonic wave is mechanical wave, and oscillation is the fundamental movement. When ultrasound passes the medium, the energy is partially absorbed [29]. In human body, the tissues and cells shake, leading to micro-massage in the body, and proposing to pain management. Low-intensity ultrasound can also enhance the dispersion of cells and the circulation of blood and lymph, and improve the tissue regeneration.

Thermal effect

Ultrasound energy absorbed by tissue causes a local temperature increase that is dependent on the ultrasound intensity, area of ultrasound beam, duration of exposure, and rate of heat removal by blood flow or conduction. The resultant temperature increase of skin and deep tissue may enhance the blood flow circulation, relax the muscle through vasodilatation, decrease the inflammation, and reduce the pain by spasm remission. The increased temperature of skin and deep tissue can also enhance the permeability due to increased diffusivity of skin, Merino et al [30] have reported the enhanced transdermal permeability caused by the increased temperature. This suggests that, the thermal energy may affect the skin permeability.

Cavitation effect

Cavitation refers to the creation of cavities as well as expansion, contraction, and distortion of pre-existing gaseous bubbles in a liquid medium [4]. Cavitation usually impacts the transdermal drug delivery. Acoustic cavitation occurs in small gaseous cavities during acoustic pressure cycles. The likelihood of cavitation occurrence is related to the ultrasound frequency and bubble characteristics such as size and shape. Cavitation can be further classified into two categories, stable cavitation and inertial cavitation, according to the activity of gaseous bubbles in relation to the acoustic field.

Stable cavitation corresponds to a continuous oscillation of bubbles around the equilibrium radius in response to relatively lower acoustic pressures in an acoustic field [31]. Bubble oscillation around asymmetric boundary conditions by stable cavitation leads to a phenomenon called microstreaming. The characteristics of microstreaming are determined by fluid properties such as acoustic attention, viscosity and density, as well as the ultrasound characteristics including temporal average intensity, frequency, transducer aperture size and pressure amplitude [32]. Theoretical and experimental study shows that microstreaming near a cell boundary can affect a cell membrane [33]. This can cause channel activation, allowing delivery of compounds for therapeutic purposes [34, 35]. Therefore, cavitation may preferentially occur within the coupling medium between ultrasound transducer and skin surface, and may locally increase the skin permeability [36-38].

Inertial cavitation corresponds to the violent growth and collapse of bubbles that can occur within a period of a single cycle or a several cycles, and is dependent on acoustic pressure as well as frequency and size of bubble [39]. Shock waves generated by inertial cavitation can cause structural alterations, resulting in creation of diffusion channels through which drugs may be potentially delivered. This leads to lipid bilayer disorder and formation of aqueous channels in the skin through which drugs can permeate [4]. Some studies have provided a general idea of temporal responses of various biologic barriers to cavitation [40, 41]. The applied ultrasound of cavitation nuclei on the skin plays a major role in enhancing cavitation effects. Adopting low frequency (e.g., 100 kHz) ultrasound is considered suitable to increase the cavitation effects in transdermal drug delivery [42].

Animal experiments

From the literatures, animal experiments involve three categories including mechanisms of sonophoresis, therapeutic intensity of ultrasound stimulation and comparison of transdermal drug delivery with or without sonophoresis. All the results are listed as the follows, and these frontier studies can provide evidence to clearly understand the principle of sonophoresis.

Hseih et al [43] report that ultrasound stimulation can impact the pain nerve system in the brain of rats, and the ultrasonic treatment can increase the nitric oxide neurons the material to help set up pain nerve [44]. The mechanism that ultrasound wave can reduce pain is regulating the neural pathways. Guo et al [45] have studied the mechanisms of sonophoresis in rabbits with osteoarthritis, comparing model and ultrasound group with the normal one. Results find that, after sonophoresis treatment, the apoptotic rate of chondrocytes is lowered, and the expressions of caspases-3 and caspases-8 are also lowered. This indicates that, ultrasound can improve the structure of cartilage tissues, decrease the expressions of caspases-3 and caspases-8 and reduce the apoptosis rate of chondrocytes. Sonophoresis is effective for the treatment of knee osteoarthritis. Du et al [46] report that, the pain relieving effect of ultrasound-medium frequency electrotherapy may be the increase of methionine encephalin in adenohypophysis. This work on sonophoresis is competed in rats.

The study on using ultrasound stimulation to facilitate regeneration after peripheral nerve injuries has been done in the rat sciatic nerve model [47]. Low-intensity ultrasound stimulation (16 mW/cm^2) is applied for 20 min a day for 12 days after sciatic nerve transection and repair. Compared with sham group, the US-treated rats have a greater quantity of regenerating nerve fibers, increased myelination, increased fiber diameter size, and increased Schwann cell activity. In another experiment, after a crushing injury to the sciatic nerve, the US-treated rats (0.25 W/cm^2, one min three times a week for 30 days) have a statistically significant acceleration of foot function recovery compared to non-treated rat nerves [48].

The studies for the advantage of sonophoresis on transdermal drug delivery are also performed on excised hairless rat skin over a period of 24 h using Franz diffusion cells [21]. Results find that, sonophoresis can significantly enhance the permeation of ketoprofen from 74.87±5.27 μg/cm^2 with passive delivery to 491.37±48.78 μg/cm^2. Furthermore, the drug level in skin layers increases from 34.69±7.25 μg following passive permeation to 212.62 ±45.69 μg following sonophoresis. The low-

intensity sonophoresis is an effective method to improve the transdermal drug delivery.

Problems in sonophoresis

Sonophoresis has been used for treating chronic pain, but the decision to use ultrasound stimulation in clinical practice after nerve and tendon injury, stroke hemiplegia, herpes zoster, acute mastitis, chronic pelvic pain should be based on the experience and guidance from the studies. Actually, we have adequate literatures, but we lack of the clinical practice. There seems to be some problems needing to be focused on, in order to promote ultrasound stimulation technique on pain management: i) For example, ultrasound stimulation (0.5-1.0 w/cm^2) to reduce symptoms of carpal tunnel syndrome. This standard is from the literature, if it is enough to treat CTS? ii) What about the therapeutic standard for other applications? Iii) What about the therapeutic standard for sonophoresis on transdermal drug delivery?

Low-frequency sonophoresis has been the topic of extensive research over the last 20 years, but the mechanisms of sonophoresis are still not clearly understood. This is the reason that we cannot set off the therapeutic standard for ultrasound stimulation. Well-designed clinical trials are necessary to study different modality applications and clarify the mechanisms.

The effects of low-frequency sonophoresis in an effort to enhance the transport of various drugs have been confirmed by some studies [49, 18]. Sonophoresis can enhance the skin permeability so that sufficient quantities of analyte can be obtained [50, 51]. Cavitation is the principle that we need to pay more attention from the literatures, and adopting low-frequency sonophoresis is one way to increase the existing cavitation bubbles [26, 52]. In the same way, the well-designed clinical trials based on different application are necessary to understand the mechanisms for acquiring the effective clinical practice.

Conclusion

Due to the applications of ultrasound stimulation and the advantage of transdermal drug delivery, there is a growing interest in sonophoresis. Numerous studies for low-frequency ultrasound stimulation have been reported. Based on these studies, the thermal mechanism and cavitation are believed to be the main mechanism of sonophoresis. Although we need more clinical trials to confirm the mechanisms in order to acquire the therapeutic standard, the results that have been performed through many comparison studies still provide a good foundation for further research.

In future work, beside we set up the therapeutic standard for different applications, the safety of sonophoresis used in the treatment should be established through a wide variety of experiments. In addition, we need develop the indication and procedure of ultrasound stimulation treatment, and the parameters such as intensity and lag time should be optimized. The skin characteristics of each body affect the efficiency of stimulation and drug delivery. Specific protocols and ultrasound parameters should differ according to different applications. There are some available studies which have examined ultrasound stimulation to pain management, but the literatures on the use of ultrasound stimulation for humans are not sufficient, the therapy standard is not established, all of these are the problems that we need to focus on. Sonophoresis is expected to be an effective method for treatment of diseases in the future, especially pain management.

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Disclosure of conflict of interest

None.

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