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https://newdaymedicine.com E:
ndmuz@mail.ru
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THE EFFECTIVENESS OF ULTRASOUND IN ACCELERATING BONE FRACTURE HEALING

[1]Ruzikulov Olimjon Shodievich https://orcid.org/0009-0008-6354-3594
[2]Dursunov Axmat Malikshayevich https://orcid.org/0000-0002-0571-0488
[3]Jurayev Ilhom Gulomovich https://orcid.org/0000-0003-1173-8572
[1]Mannonov Anvar Abduvakil o'g'li https://orcid.org/0009-0000-5038-3618

[1]Republican Specialized Traumatology and Orthopedics Scientific and Practical Medical Center, Taraqqiyot Street, 78, Tashkent city, 100047, phone: +998 (71) 232-20-89 https://uzniito.uz/
[2]Samarkand branch Republican Specialized Scientific and Practical Medical Center of Traumatology and Orthopedics, 140107, Uzbekistan, Samarkand region, City: Samarkand, st. Kozi Zoda Rumi, 73 Email: samtravmatologiyasentr@mail.ru
[3]Samarkand State Medical University Uzbekistan, Samarkand, st. Amir Temur 18, Tel: +99818 66 2330841 E-mail: sammu@sammu.uz

✓ ***Resume***

Low-intensity pulsed ultrasound (LIPUS) is an emerging technology that has been shown to enhance the fracture healing process with minimal thermal effects. This non-invasive treatment accelerates bone formation through various molecular, biological, and biomechanical interactions with tissues and cells. Although LIPUS treatment has demonstrated beneficial effects on different bone fracture sites, very few studies have investigated its effects on deeper bones. LIPUS is a type of ultrasound that is transmitted into connective tissues as an acoustic wave. As a non-invasive therapy, LIPUS has been utilized to promote fracture healing for 30 years and is the subject of numerous clinical studies. LIPUS can stimulate the differentiation of bone-forming cells, which contribute to bone formation, fracture healing, and the recovery of strength at the healing site. It has been established that LIPUS can promote the formation of the medullary canal and cortex in a gap-healing model, leading to earlier restoration of the structural integrity of the healing site. Many clinical studies indicate that LIPUS can enhance the healing of fresh fractures, delayed unions, nonunions, distraction osteogenesis, and congenital pseudoarthroses

Key words. Ultrasound, fracture healing, nonunion, osteogenesis

ЭФФЕКТИВНОСТЬ УЛЬТРАЗВУКА В УСКОРЕНИИ ЗАЖИВЛЕНИЯ ПЕРЕЛОМОВ КОСТЕЙ

Рузикулов О.Ш.[1] Дурсунов А.М.[2], Жураев И.Г.[3], Маннонов А.А.[1]

[1]Республиканский специализированный научно-практический медицинский центр травматологии и ортопедии, улица Тараккиет, 78, г. Ташкент, 100047, телефон: +998 (71) 232-20-89 https://uzniito.uz/
[2]Самаркандский филиал Республиканский специализированный научно-практический медицинский центр травматологии и ортопедии, Республики Узбекистан, Ташкент 140107, Узбекистан, Самаркандская область, Город: Самарканд, ул. Кози Зода Руми, 73 Email: samtravmatologiyasentr@mail.ru
[3]Самаркандский государственный медицинский университет Узбекистан, г. Самарканд, ул. Амира Темура 18, Тел: +99818 66 2330841 E-mail: sammu@sammu.uz

✓ ***Резюме***

Низкоинтенсивный импульсный ультразвук (LIPUS) — это новая технология, улучшает процесс заживления переломов с минимальными термическими эффектами. Это неинвазивное лечение ускоряет формирование костей посредством различных

молекулярных, биологических и биомеханических взаимодействий с тканями и клетками. Хотя лечение LIPUS продемонстрировало благоприятное воздействие на различные участки переломов костей, очень мало исследований изучало его воздействие на более глубокие кости. LIPUS — это тип ультразвука, который передается в соединительные ткани в виде акустической волны. В качестве неинвазивной терапии LIPUS используется для содействия заживлению переломов в течение 30 лет и является предметом многочисленных клинических исследований. LIPUS может стимулировать дифференциацию костеобразующих клеток, которые способствуют формированию костей, заживлению переломов и восстановлению прочности в месте заживления. Было установлено, что LIPUS может способствовать формированию костномозгового канала и коркового вещества в модели заживления щелей, что приводит к более раннему восстановлению структурной целостности места заживления. Многие клинические исследования показывают, что LIPUS может улучшить заживление свежих переломов, замедленных сращений, несращений, дистракционного остеогенеза и врожденных псевдоартрозов

Ключевые слова. Ультразвук, заживление переломов, несращение, остеогенез

SUYAK SINISHINI DAVOLASHNI TEZLASHTIRISHDA ULTRATOVUSHNING SAMARADORLIGI

[1]*Ruzikulov Olimjon Shodievich,*[2]*Dursunov Axmat Malikshayevich,* [3]*Jurayev Ilhom Gulomovich*
[1]*Mannonov Anvar Abduvakil o'g'li*

[1]Respublika ixtisoslashtirilgan travmatologiya va ortopediya ilmiy-amaliy tibbiyot markazi, 100047, Toshkent shahar, Taraqqiyot ko'chasi, 78-uy tel:+998 (71) 232-20-89 https://uzniito.uz/
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[3]Samarqand davlat tibbiyot universiteti O'zbekiston, Samarqand, st. Amir Temur 18, Tel: +99818 66 2330841 E-mail: sammu@sammu.uz

✓ ***Rezyume***

Past intensivlikdagi impulsli ultratovush (LIPUS) - bu minimal issiqlik effektlari bilan sinishni davolash jarayonini kuchaytirishi ko'rsatilgan rivojlanayotgan texnologiya. Ushbu invaziv bo'lmagan davolash to'qimalar va hujayralar bilan turli molekulyar, biologik va biomexanik o'zaro ta'sirlar orqali suyak shakllanishini tezlashtiradi. LIPUSNI davolash turli xil suyak sinish joylariga foydali ta'sir ko'rsatgan bo'lsa-da, juda kam tadqiqotlar uning chuqur suyaklarga ta'sirini o'rgangan. LIPUS-bu akustik to'lqin sifatida biriktiruvchi to'qimalarga uzatiladigan ultratovush turi. Invaziv bo'lmagan terapiya sifatida LIPUS 30 yil davomida sinishni davolashni targ'ib qilish uchun ishlatilgan va ko'plab klinik tadqiqotlar mavzusi hisoblanadi. LIPUS suyak hosil qiluvchi hujayralarning differentsiatsiyasini rag'batlantirishi mumkin, bu suyak shakllanishiga, sinishni davolashga va shifo joyida kuchni tiklashga yordam beradi.

LIPUS shakllanishiga yordam berishi mumkinligi aniqlandi medullar kanali va korteks bo'shliqni davolash modelida, shifo joyining tarkibiy yaxlitligini ilgari tiklashga olib keladi. Ko'pgina klinik tadqiqotlar shuni ko'rsatadiki, LIPUS yangi yoriqlar, kechiktirilgan uyushmalar, birlashmalar, chalg'ituvchi osteogenez va tug'ma psevdoartrozlarni davolashni kuchaytirishi mumkin

Kalit so'zlar. Ultratovush, sinish shifo, nonunion, osteogenez

Relevance

The therapeutic use of ultrasound began in the early 1930s.1 Initially, a frequency of 800 kHz and an intensity between 4000 and 5000 mW/cm² were employed in the treatment of neuralgia, myalgia, and other conditions. The higher intensity of ultrasound resulted in increased heating of biological tissues [1,2]. In the 1940s, ultrasound treatment was primarily used for young bones in humans and dogs [3]. It faced criticism for potentially causing bone damage until Barth,4 discovered that low doses of ultrasound did not adversely affect bone or surrounding tissues.

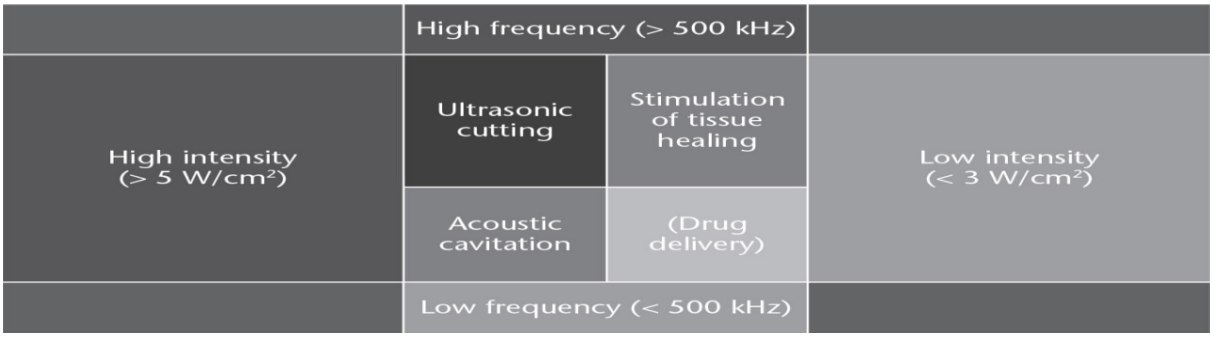
Meanwhile, other early clinical studies indicated that ultrasound stimulation at higher intensities, ranging from 5000 to 25000 mW/cm², led to complications such as necrosis, halted bone healing, and the formation of fibrous tissue [5,6]. It was also noted that ultrasound could stimulate osteogenesis.7 Maintz utilized ultrasound at low intensities, between 500 and 2000 mW/cm², for treatment in the limbs of rabbits and observed the formation of new periosteal bone [8]. The first successful formation of new callus at fracture sites was achieved using continuous ultrasound stimulation at an intensity of 1500 mW/cm² [9]. To minimize thermal effects on soft tissues, it was suggested to use low-intensity and pulsed ultrasound signals for stimulation, which resulted in bone growth in the tibia of rabbits at an intensity of 200 mW/cm² [10].

Low-intensity waveforms are designed to stimulate physiological responses to injury or to accelerate certain biological processes, while high-intensity treatments aim to selectively destroy tissues. In this area, a broad spectrum of ultrasound frequencies has been utilized, ranging from approximately 20 kHz to several MHz; frequencies below a few hundred kHz are typically classified as 'low-frequency ultrasound,' whereas frequencies around 1 MHz and above are generally referred to as 'high-frequency ultrasound.' Higher-power ultrasound at lower frequencies (20 kHz to 100 kHz), known as 'power ultrasound,' can induce microbubble formation, also termed cavitation. The resulting interaction between biological tissues and the waveform can be characterized as thermal or nonthermal [8].

Materials and methods

The energy carried by an ultrasonic beam diminishes as it travels through biological tissue. This energy loss is attributed to scattering of the ultrasonic beam and absorption by extracellular fluid, leading to a heating effect. The high absorption coefficients of large protein molecules indicate that collagenous tissues, such as cortical bone, myofascial junctions, tendon sheaths, fibrotic muscle, and major nerve trunks, may experience preferential heating. The degree of physiological response to heating depends on the peak temperature, rate of temperature increase, duration of heating, and the volume being heated [4].

Nonthermal (mechanical) effects Nonthermal mechanisms that can induce therapeutic changes in biological tissues may be cyclical or noncyclical. Reported macroscopic cyclical effects include local hemodynamic changes and angiogenesis [6,7]. Mechanical effects of ultrasound at the cellular level include stimulation of cell proliferation [10] cell membrane depolarization, and mast cell degranulation [11].



The use of low-intensity pulsed ultrasound as an adjunct in the management of fracture healing acceleration in fresh fractures and delayed/nonunions is controversial. It has been reported to induce the proliferation of preosteoblast-like bone cells [7] and the differentiation of mesenchymal stem cells towards osteogenesis [8]. Further in vitro studies have demonstrated that ultrasound stimulation in osteogenesis occurs through mechanotransduction of osteocytes and osteoblasts via integrin-signaling pathways [9] and Piezo ion channels, leading to an enhanced local acute inflammatory environment and subsequent fracture healing [10]. A more recent systematic review and meta-analysis, using criteria for defining fracture nonunion as no evidence of radiological union at least three months post-injury, investigated the effects of low-intensity pulsed ultrasound in 1441 fracture nonunions [15]. It concluded that ultrasound could be an alternative to surgery for established aseptic nonunions, with over 80%

achieving union. Hypertrophic nonunions were found to benefit more than biologically inactive atrophic nonunions. An interval without surgery of more than six months prior to ultrasound treatment was associated with a more favorable result. Studies reported that ultrasound stimulation enhances bone formation by accelerating the process at the inflammatory stage and 11 subsequent phases of fracture healing [12,13]. Ultrasound stimulation for the human body is safe and noninvasive.

LIPUS therapy has been widely accepted for enhancing endochondral bone formation [14]. It has also been shown to increase blood flow near the injured area and reduce healing time in cases of scaphoid fractures, tibial fractures, and distal radius fractures [15]. The therapeutic ultrasound used in LIPUS is safe and does not require any subsequent surgeries, [16] and higher treatment efficiency can be achieved when it is applied in the initial stage of the fracture. Additionally, LIPUS treatment can be used alongside metallic fixtures without causing any adverse effects to the tissues. Fractures less than 1 week old are considered fresh fractures [17]. It is clinically proven that LIPUS plays an important role in the healing of fresh fractures with an ultrasound intensity of 30 mW/cm^2. LIPUS has demonstrated positive effects on patients regardless of age, smoking status, fracture gap, and the absence of fibular fractures as well as distal fracture location. Furthermore, some studies have reported that LIPUS did not reduce healing time or functional recovery with metallic fixations. LIPUS is more suitable for nonoperative treatments because there is a higher risk of osteonecrosis during operative treatments.

Results and discussions

It has been found that the efficiency of bone union with LIPUS treatment is closely related to the time interval between the most recent surgery and ultrasound treatment, which should be less than 3 months [18]. Additionally, it has been shown to be more effective in treating postoperative nonunions when LIPUS therapy is initiated within 6 months after surgery [19]. It has also been reported that LIPUS is an effective approach for acute fractures such as long bones, particularly in cases of nonunions [20]. It appears that better bony union can be achieved if treatment is initiated at the appropriate time following fracture events. However, there have been no reports indicating that Low-Intensity Pulsed Ultrasound (LIPUS) in cases of nonunion shows any improvement in weight-bearing ability, pain reduction, or a decrease in the time required for radiographic healing. In addition to timing, a recent study on established nonunions demonstrated that LIPUS treatment for bone healing also depends on factors such as the type of fracture and the treatment approach to the injury. Therefore, LIPUS is effective in distraction osteogenesis by reducing the consolidation period. The main drawback of this method is that it is time-consuming, as the consolidation phase in distraction osteogenesis can last up to six months, resulting in an extended treatment period, which also varies depending on the size of the bone defect. LIPUS influences the mechanical properties of bone by increasing bone density. It has been suggested that LIPUS affects certain factors, including collagen cross-linking, collagen alignment, and porosity, which determine the mechanical properties of bone [21]. LIPUS treatment on the mid-tibia of rabbits that underwent osteotomy with a fixator produced significant improvements in callus mineral density by the end of the eighth week, but no significant effect on the flexural strength of the fractured bone was observed [22]. Overall, it has been clearly demonstrated that LIPUS stimulation aids in improving the mechanical properties of bone during the fracture healing process. During the inflammation and callus formation stages, ultrasound enhances the deposition of certain proteins such as collagen and aggrecan. When ultrasound waves are transmitted to the bone through the surrounding tissues, the cells near the fracture site convert the biomechanical stimulation into a biochemical response via integrins, which are crucial molecular mediators in sensing mechanical signals. A cadaveric experiment demonstrated that bone responds to mechanical stimulation and displacement, a phenomenon known as “micromotion” [23]. Another potential biological effect of ultrasound stimulation is the creation of mechanical stress in tissues, which further promotes osteogenesis, protein synthesis, calcium uptake, and DNA synthesis in various cell types.

Conclusion

Low-intensity pulse ultrasound stimulation could accelerate the healing of fractures in the distal radius and promote local bone formation. Moderate to high-quality evidence indicates that LIPUS does not speed up the return to work, the return to full weight bearing, or pain reduction, nor does it decrease the need for subsequent surgeries. The role of ultrasound as a therapeutic adjunct in managing fracture nonunions remains unclear and is under ongoing scrutiny.

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