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Review Article

The role of biophysical enhancement (LIPUS, ESWT and PEMF's) in fracture healing

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Abstract

Fracture healing is a biological route that may not always lead to bone healing. Delayed union or even nonunion of a fracture is possible to have devastating socio-economic impact on patients and healthcare systems. Except of surgical treatment, other non-invasive methods have been proposed for the management of non-united fractures commonly known as biophysical enhancement. This includes low-intensity pulsed (LIPUS), extra-corporeal shockwave therapy (ESWT) and pulsed electromagnetic fields (PEMF) stimulation. The utility and efficacy of biophysical enhancement is a matter of question and no safe conclusion can be drawn especially because of great heterogeneity present in literature.

Keywords: ESWT, Fracture healing, LIPUS, Nonunion, PEMF

Introduction

Fracture healing is a unique mechanical and biological process which may sometimes unfortunately lead also to delayed union or even nonunion. The incidence of this phenomenon is reaching 5-10% in literature depending on fracture site and type. There are no standard universally acceptable criteria to define nonunion[1,2]. According to the United States Food and Drug Administration (FDA) a nonunion is defined as a fracture that has not completely healed within few months post injury, with serial radiographs demonstrating no progression of healing during the last months. Taking into consideration that in the United States the number of fractures is reaching 7.9 million every year, it is widely accepted that fracture-healing complications have a significant health-care cost as well as socioeconomic cost and quality of patient-life impact. This is particularly true for fractures of long bones and also differences exist when taking into consideration weight bearing bones (femur, tibia) rather than non weight bearing ones (humerus, ulna, radius)[3].

Nonunion is classified in hypertrophic, oligotrophic and atrophic in correspondence with the amount of callus that is formed. Mechanical stability, cellular environment, growth factors, bone matrix and vascularization affect mostly the outcome of this process. Nonunion may occur when a fracture is managed conservatively but also when treated surgically. The ending status of a nonunion is the formation of a synovial pseudarthrosis with the distinction between these two coming from the presence of pain in the area of fracture. This fracture complications have low or no potential of spontaneous healing and their treatment is a challenging clinical scenario for the orthopedic surgeon[3].

The gold standard surgical treatment for delayed union/nonunion is autologous bone grafting and revision of the osteosynthesis (internal or external), if they were operated previously, to provide adequate stabilization and decortication of bone ends. Using these techniques biology and mechanical structure of the bone are restored. However, revision surgery for established nonunion is technically demanding, enclosing its own risks and complications. The surgical treatment is usually associated with additional hospitalization, comorbidities from the surgical procedure, and significant socioeconomic costs. In an effort to decrease

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patient morbidity and health care costs, several of non-invasive methods have been tested for the treatment of delayed union and nonunion.

Biophysical enhancement in fracture healing including low-intensity pulsed (LIPUS), extra-corporeal shockwave therapy (ESWT) and pulsed electromagnetic fields (PEMF) stimulation have been also suggested for the management of non-united fractures.

Methods

An electronic search via the PubMed search machine was initially performed. Inclusion criteria were articles in the English language, published within the previous 20 years, concerning treatment of nonunion of fractures in humans with usage of biophysical enhancement. We excluded studies performed in animals. Key words used were: (shockwave AND fracture), (electromagnetic AND fracture), (ultrasound AND fracture). The search was further extended manually to the reference section of all articles involved. Two investigators (IDA, PKM) independently extracted the relevant data. Disagreement between reviewers was resolved by discussion.

Results

According to our inclusion and exclusion criteria, thirty-nine studies were found to be eligible and are included in this review. Relevant studies for each technique are briefly presented below.

Extra-corporeal shockwave therapy (ESWT)

In the past decades there has been a lot of discussion concerning the beneficial effects of ESWT for the treatment of fractures. Especially delayed or non-healing fractures collect bigger scientific interest because of the complications that they are connected with. ESWT mechanisms is not clearly proved but there is evidence that their use is based in transformation of mechanical waves into biomechanical signs. Pressure waves created as result of piezoelectric, electromagnetic or electrohydraulic field seem to affect intracellular pressure in tissue cells. This procedure causes growth factor cascade with angiogenic and osteogenic results[4,5]. ESWT has been tested for different types of bone fractures long or not. Even more discussion there is about the dosage.

Kuo et al. in 2015, in their study analyzed a population of 22 patients and compared early application of ESWT (within 12 months from operation) with application later than 12 months. All patients suffered from femoral fractures with atrophic nonunion and where treated with closed reamed intramedullary nailing. They described a union rate 100% concerning early application while later application produced 42.9% union rate[6].

The same healing results come from another research that studied tibial nonunion fractures initially surgically treated. They showed a healing rate of 88.5% after 6 months irrespective of the type of the nonunion (hyperthrophic, oligotrophic/atrophic, infection) and the underlying pathology[7].

The effectiveness of ESWT on atrophic and hypertrophic nonunion differs among studies. Some of them suggest that there is no difference while others indicate that there are better results when ESWT is applied on hypertrophic nonunion[7,8].

Schaden et al. in 2015, in their review summarized how ESWT can be as beneficial as reoperation regarding healing time, cost and complications[5]. They included different studies with patients with various types of fractures such as fractures of the fifth metatarsal bone, carpal scaphoid, and long bone fractures. There were differences in the amount of dose and in the number of sessions but not in the healing rates. More specific ESWT application gave 91% rate versus 90% for the reoperation as far as the fifth metatarsal is concerned, for the scaphoid the same numbers are 79.3% versus 78.3% and for the long bone category it is 92-94% (dose depending) versus 95%[9-11].

In another study Wang et al. in 2007, focused on the immediate to operation application of ESWT[12]. Griffin et al. in their review found satisfactory outcomes of ESWT treatment in acute fractures, applied at 3,6 and 12 months regarding union rate, weight bearing and pain and[13].

This technique seems to be helpful in treating less severe or prefracture conditions such as medial tibial stress syndrome (MTSS) as it is described in a small case series study[14].

Pulsed Electromagnetic Fields (PEMFs)

PEMF's as a safe and non invasive method is thought to enhance osteogenesis by activating osteogenic markers. Its beneficial effect on bone biology is well described in many studies but with controversial results. Even though a definitive mechanism of action has not been proposed for PEMFs, it seems that external stimulation of ions force them to move towards the electric fields. Ions' interaction with the cell membrane induces chemical and biochemical changes. Various signaling pathways have been described including Ca^{2+}, Wnt/β-catenin, MAPK, FGF and VEGF, TGF-β/BMP and IGF that promote angiogenesis and osteogenesis. It has been used on both delayed union and nonunion and acute fractures and also on adults, adolescents and children. The complexity of the fracture healing pattern requires specific principles of PEMFs as far as frequency, intensity and dose are concerned[15,16].

According to Assiotis et al. in 2012 and Shi et al. in 2013 long bone fractures seem to improve their rate of healing with the appliance of PEMF's. The first study summarizes results from 44 patients (mean age 49,6±18,4 yo) with tibial shaft non union and fracture gap less than 1 cm. Although this improvement is not statistically significant there seems to be a trend of increased possibility of union ($p=0.081$)[17].

The second study includes 58 patients with femoral, tibial, humeral, radius and ulnar fractures diagnosed with delayed union and divided in treatment and control group. Use of PEMFs in comparison with placebo group gave a union rate of 77,4 % in contrast with 48,1% for the control group (p=0,029)[18]. Same findings come from another study of Streit et al. in 2016, concerning 5th metatarsal delayed or nonunion. In this study they evaluated two parameters: the radiographic signs of union (four cortices) and the levels of growth factors that enhance bone healing. There was a mean healing rate of 8.9 weeks for the study group against 14.7 weeks in the control group and moreover statistically significant higher level of placenta growth factor (p=0,043)[19].

PEMF's has been widely used to accelerate fracture repair not only as an alternative to surgery for nonunion but also for the treatment of acute fractures. Scaphoid and radial fractures consist the majority of wrist injuries affecting many patients. These two separate anatomical structures have significant differences in healing pattern due to the varying type of blood supply. Hannemann et al. in 2012 and Lazovic et al. in 2012 agreed that there was a not statistically significant difference in radiological outcomes although there is a beneficial trend. Swelling, edema and function of the wrist also seem to have better results in patients treating with PEMF's[20,21].

Electromagnetic stimulation for surgically treated femoral fractures (intramedullary nailing) can be used as a conjugant in the healing process. In a two-center randomized control trial Martinez et al. in 2014 suggested that there was earlier bone healing with the use of PEMF's in acute phase compared to placebo for diaphysial fractures of the femoral[22].

In the pediatric population although non unions of the fractures or osteotomies are not common the use of PEMF's may have a role in their treatment. According to Boyette et al. minimal invasive techniques such as PEMF's combined or not with bone grafting seem to reduce time needed to bone healing. This is translated into earlier weight bearing which permits sooner return to everyday activities[23].

Meta-analyses and reviews have been carried out concerning this controversial topic[24-27]. Even though they included small and methodologically limited trials they concluded that electrical stimulation does trend in favour of helping fracture healing. This trend is not of statistical importance for acute fractures, delayed unions, non-unions and osteotomies.

Low Intensity Pulsed Ultrasound (LIPUS)

Another biophysical intervention commonly used for fracture healing is low intensity pulsed ultrasound (LIPUS). Soundwaves generated during this procedure cause micromechanical stress that stimulates cellular and molecular changes at the fracture site. LIPUS induces alkaline phosphatase levels and other osteogenic genes leading to angiogenic and osteogenic response[28]. This method seems to be effective in nonunion and as an acute strategy for bone healing for a various kind of fractures.

To reinforce the statement that LIPUS acts beneficially on callus formation there has been research on histological parameters suggesting that histomorphometric bone characteristics are increased in LIPUS-treated delayed unions. This technique cannot change the vessel number but augments the blood vessels in size[29,30]. Moreover LIPUS increase osteoblastic activity and this affects osteoid thickening, mineral apposition rate and bone volume[30].

A recent study of 61 patients has shown a short healing rate (32.8%) concerning long bone nonunion fractures treated with LIPUS (EXOGEN)[31]. Additionally, Nosaka et al. in 2004, in a single case of femoral shaft fracture had significant radiographic and clinical signs of healing 3 months after the use of ultrasound combined with human parathyroid hormone (teriparatide)[32]. Of course, teriparatide is a bone agent known to promote bone formation and even bone healing as shown in various research papers, and the single effect of LIPUS when applied with teriparatide cannot be estimated in such a study. All these indicate that the choice about the application of LIPUS should be performed individually case by case. As far as cost-effectiveness is concerned this technique seems to provide an at least 60% reduced cost than the traditional decortications technique[33]. The factors that affect crucially the outcomes of the LIPUS therapy are the stability of the callus site, the characteristics of the nonunion and the gap size[33,34]. More specific in their study Watanabe et al. proved that hypertrophic nonunion had much better healing rate than oligotrophic and atrophic ($p<0,01$). Fixation that provided a stable environment in the site of fracture gave better therapeutic results ($p<0,001$). But the most decisive point that influences the healing process seems to be the gap size ($p<0,0001$)[34].

The stimulation of bone formation for scaphoid fractures with ultrasound waves has been investigated in a randomized control trial of 30 patients by Mayr et al. In this study there was a statistically significant difference in the time to radiographic callus formation for the LIPUS treatment group (30% less time)[35]. Same encouraging outcomes have been shown in another research in which is suggested that early diagnosed scaphoid fractures tend to have better healing rate than lately diagnosed (p=0,06) irrelevant OF the location of the scaphoid fracture. Even though this doesn't differ statistically it notes a clear trend[36].

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To determine whether LIPUS accelerate radiographic healing and functional recovery in patients with tibial fractures treated operatively Busse et al. in 2016 organized a RCT. They concluded that there was no difference in time to healing as it is depicted in x-rays and there was no significant difference in functional recovery[37].

For acute treatment concerning fractures of the upper limp findings are still controversial. On the one hand, Liu et al. in 2006, in their study found that radial fractures had shorter healing time with the use of ultrasound ($p<0,01$)[38]. On the other hand Lubbert et al. in 2008 with their multicenter RCT proved that there was no difference in clinical healing time and return to everyday activities, sports and work[39]. For these patients pain tolerance and reception of painkillers measured by pain scores was not affected[39,40].

Another aspect that is to investigate is the feasibility of this treatment as far as the cost is concerned. Tarride et al., with a 501 patient trial documented that LIPUS is not cost effective for fresh tibial fractures treated with intramedullary nailing[41].

Through the past decades many systematic reviews and meta-analyses have been conducted to identify the effect of ultrasound on fracture healing. Among these heterogeneous studies there are areas of agreements and areas of controversy. For acute fractures treated with cast LIPUS play an important role improving time to healing and quality of life without affecting the incidence rate of union[25,42,43]. Furthermore bone healing in fresh fractures operatively treated can be stimulated by ultrasounds[44].

According to Leighton et al., LIPUS is associated with a very high overall success rate (>80%) that is comparable to the rate of surgical treatment of not infected nonunion. This technique can be an alternative to surgery not only for established non unions but also can be useful in high risk patients. It could be a coadjuvant in treating elderly people with dementia, cardiovascular and/or respiratory comorbidities and even more in patients with extensive soft tissue trauma. Despite the fact that LIPUS doesn't improve mechanical stability it seems to be more beneficial in hypertrophic nonunion than in oligotrophic or atrophic nonunion. Even more, against common surgical strategy, LIPUS seems to have more favorable intervention when it is used as an alternative rather than as a coadjuvant to operation. Another factor that is important on the success rate of nonunion is that LIPUS results are better when applied 3-6 months after the last surgical intervention[45].

Radiographic healing and return to everyday duties for military uniform patients with tibial stress fractures preserved no improvement with the use of LIPUS[46]. Controversial results come from studies that involve the application of ultrasounds with operatively managed distraction osteogenesis. For a follow up period of 30 days LIPUS had no effect on bone formation[47]. On the other hand after 30 days of LIPUS use bone index was similar to 48 days postoperatively in the control group[46,47]. Mineral density seems to be also enchanted in the distraction callous for patients with opening wedge high tibial osteotomy[48].

Conclusion

According to our research in the published literature ESWT efficacy is a matter of debate among different studies. Their application on hypertrophic non union seems to be beneficial as this outcome comes from a better union rate but without statistical significance. This trend is not supported widely as far as there are studies that suggest no differences as far as the usefulness is concerned.

Questionable results come up from literature for the role of PEMF's in bone healing. Although there is a beneficial trend this is not of statistical importance in most studies. Healing rate time seems to be reduced when PEMF's are combined with placenta growth factor.

Heterogeneity of studies permits no safe conclusion for LIPUS usage. Acute fractures and non unions without infection seems to be more benefited. Lipus treatment as an adjuvant therapy seems to provide better results in hypertrophic non unions, in stable fracture environment, and in cases with smaller gap size with statistical significance.

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