Trauma: Non-Union: New Trends

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Introduction

Fracture healing is a complex physiological process caused by the interaction of cellular elements that are activated and controlled by an array of cytokines and signalling proteins [11]. This process is both temporal and spatial in nature and usually results in the formation of new bone, which is structurally and mechanically similar to the pre-fracture state [10].

For al lot of reasons this process can fail and result in non-union of bone in 10% of all fractures and in up in 50% of open fractures of the tibia. These patients develop a non-union, which leads to long-lasting inability to work, loss of employment and high social costs. These cost are estimated in a paper of Sprague 2002 to be at approximately $80,000 in case of 18 weeks delay of fracture healing [28]. The overall costs of delayed fracture healing are estimated to be at $14.6 million in United States alone [6].

Many attempts have been made to reduce the rate of disturbed fracture healing but despite the correct osteosynthesis, which is mandatory, and new improved interlocking plates, biologic osteosynthesis and improved surgical techniques like subcutaneous plating, the overall rate has not been reduced. The standard procedure to induce or enhance bone healing in a delayed status is autologous bone grafting. This procedure provides osteogenic, osteoinductive and osteoconductive properties and has a success rate of 50–80% [7, 9, 29, 33]. But the success of this "gold standard" depends on the quality of the harvested bone and is naturally limited by the amount available from the donor.

Nowadays it could be stated, that correct technical debridement and knowledge about "correct osteosynthesis" is the basic treatment and the rules of stability have to be implemented. But there are some new possibilities which can help as an adjunct to increase the healing rate of fractures and/or non-unions.

New trends are:

Low Instensity Pulsatile Ultrasound (LIPUS)

Ultrasound treatment of a non-union or delayed union is dependent on specific pre-requisites. First the fracture or non-union has to be mechanically stable which is not often the case in non-union. Secondly, the non-union has to viable. But most of the non-unions or fractures at-risk have exactly this problem and today the non-invasive diagnosis is very difficult to determine if a non-union is atrophic, oligotrophic or hypertrophic. Therefore the indication for conservative treatment with pulsatile ultrasound is also very limited.

But, if it is possible, it seems that it is sometimes successful.

In prospective, randomized, double-blind, placebo-controlled, multi-centre clinical studies, LIPUS has been proven to be effective in decreasing the time to heal in both fresh diaphyseal (tibia) and metaphyseal (distal radius) fractures. It also decreases the likelihood of a delayed union (>150 days to heal) in tibial fractures and loss of reduction in distal radius fractures. World-wide clinical studies of LIPUS for treatment of non-union, in a self-paired control study design, have demonstrated a healing rate of 88% with an average treatment time of 4.5 months in non-unions and an average fracture age of 23 months. The therapy is safe and non-invasive, and is used by the patient at home for a 20-min treatment session per day [8].

In a study of Jingushi, seventy-two cases of long bone fracture, including those of the femur, tibia, humerus, radius, and ulna, were analyzed. The mean time from the most recent operation to the beginning of LIPUS treatment was 11.5 (3–68) months. The relationship between the background factors and the union rate was analyzed

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using a logistic regression method. In addition, long bone fractures in an upper extremity or in a lower extremity were analyzed separately. The union rate was 75% in all the cases of long bone fracture. There was a significant relationship between the union rate and the period from the most recent operation to the beginning of LIPUS treatment in all cases and in those that had long bone fracture of an upper extremity. There was also a significant relationship between the union rate and the time when a radiological improvement was first observed after the beginning of the treatment in all cases and in those with fractures in a lower extremity. When LIPUS treatment was started within 6 months of the most recent operation, 89.7% of all fractures healed. When an improvement in the radiological changes at the fracture site was observed after 4 months in those cases, then the sensitivity and specificity for union were more than 90%. Jingushi concluded that LIPUS treatment should be started within 6 months of the most recent operation. Because LIPUS has been shown to be effective without causing either serious invasiveness or any undue risk to the patient, it may be considered the treatment of first choice for cases of post-operative delayed union or non-union [17, 18].

LIPUS also appears as an effective and safe home treatment of aseptic and septic delayed-unions and non-unions, with a healing rate ranging from 70 to 93% in different, non-randomized, studies. Advantages of the use of this technology are: that it may avoid the need for additional complex operations for the treatment of non-unions and also efficacy, safety, ease of use and favourable cost/benefit ratio. Outcomes depend on the site of non-union, time elapsed from trauma, stability at the site of non-union and host type [19, 24].

The detailed biophysical process by which low-intensity pulsed ultrasound LIPUS stimulates bone regeneration still remains unknown, although various effects on bone cells in vitro and in vivo have been described.

LIPUS treatment has led to increased callus area and accelerated return of bone strength following fracture. Histological studies suggest that LIPUS influences all major cell types involved in bone healing, including osteoblasts, osteoclasts, chondrocytes and mesenchymal stemcells. The affect of LIPUS seems to be limited to cells in soft tissues, whereas cells in calcified bone seem not to be effected. In vitro cell culture studies as well as tissue culture studies have shown some effects on cell differentiation and protein synthesis. Even though the energy used by LIPUS treatment is extremely low, the effects are evident. The most probable source of the therapeutic benefits observed with LIPUS treatment involves non-thermal mechanisms that influence cell membrane permeability and increase cellular activity. Despite clinical and experimental studies demonstrating the enhancing effect of LIPUS on bone regeneration, the biophysical mechanisms involved in the complex fracture healing process remain unclear and require further research [4, 19].

Magnetic Field Induction

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Electric and electromagnetic fields are, collectively, one form of biophysical technique which regulate extracellular matrix synthesis and may be useful in clinically stimulating repair of fractures and non-unions. Pre-clinical studies have shown that electric and electromagnetic fields regulate proteoglycan and collagen synthesis in models of endochondral ossification, and increase bone formation in vivo and in vitro. A substantial number of clinical studies have been done that suggest acceleration of bone formation and healing, particularly osteotomies and spine fusions, by electric and electromagnetic fields. Many of these studies have used randomized, placebo-controlled designs. In osteotomy trials, greater bone density, trabecular maturation, and radiographic healing were observed in actively-treated, compared with placebo-treated patients. In spine fusions, average union rates of 80–90% were observed in actively-treated patients across numerous studies compared with 65–75% in placebo-treated patients. Uncontrolled, longitudinal cohort studies of delayed and non-unions report mean union rates of approximately 75–85% in fractures previously refractory to healing. The few randomized controlled studies in delayed and non-unions suggest improved results with electric and electromagnetic fields compared with placebo treatment, and equivalent to bone grafts [13].

There is a consensus that electromagnetic stimulation is an effective adjunct to conventional therapy when used in the management of non-union of long bone fractures [5].

Growth Factor Treatment

Bone Morphogenetic Protein 7 (BMP 7, Osigraft™) has been shown in a prospective randomised human trial to be a cytokine which can induce bone formation in tibial non-unions at the same rate autologous bone graft [9]. BMP's are members of the Transforming Growth Factor Beta (TGF β) superfamily and are characterised by immense osteoinductive potential. They induce a sequential cascade

of events for chondro-osteogenesis during bone formation and ultimately fracture healing, including chemotaxis, proliferation of mesenchymal and osteoprogenitor cells and their differentiation into a chondrogenic or osteogenic lineage [10, 11, 26, 30, 31].

But not only BMP and TGF β are cytokines which trigger and are leading the normal process of bone healing. Today there are over 120 cytokines, growth factors hormones and other factors are known, which play a role in this process. Most of them are more or less involved but there are some key proteins like PDGF, IGF, VEGF and FGF which are known to have significant influence on the fracture healing process if they are supplemented.

Beside mechanical insufficiencies in treating fractures, it is obvious that also biological deficiencies can result in non-union.

Some clinically relevant studies can be found via Medline [4, 23, 25, 32, 34]. An overview is given in Table 1. In England, an overview of clinical BMP 7 application in all long hollow bones has recently been published. Of 653 documented cases, 60.5% had the application indicated for pseudoarthroses. In 74%, an autologous bone graft was also performed. In 23%, BMP 7 had been implanted without autologous bone transplantation. All cases that healed based upon radiological and clinical analyses without requiring further treatment were considered successful, and the success rate was 82%. Details concerning location of the fracture, the number of previous therapies, other diseases of the patients or the duration of the healing process are not reported [12].

For BMP 7, one prospective, randomized and partly-blind clinical study exists, which describes 122 patients who had been treated over a period of 7 years in 7 different trauma centres in the USA. Criterion for inclusion in the study was tibial pseudoarthrosis of at least 9 months duration. The planned surgical techniques had to be intramedullary nailing and autologous bone grafting. The control group also received intramedullary nailing, but BMP 7, instead of autologous bone, was implanted. Nine months after treatment, the success was evaluated according to the clinical criteria of being full weight-bearing and radiological fusion. The success rate in the autologous bone grafting group was 84%, and that of the BMP 7 application group was 75%. This difference was not statistically significant ($p=0.218$). In a sub-group of patients, which included those with nicotine abuse, BMP 7 showed a markedly higher success rate compared to autologous bone grafting. In addition, the frequency of infections was lower when BMP 7 was implanted. Since these were not the criteria the study was designed for, the results could not be interpreted as significant [9].

Table 1 Clinical not randomised studies using BMP 7

Author	Study design	Indication	Patients	BMP	Union rate %
Giannoudis et al. [25] UK	Retrospective, observational, non randomized	Non-union, osteotomies etc. various sites	653	7	82
Dimitriou et al. (2005)	Retrospective, observational, non randomized	Non-union various sites	26	7	92
Ronga et al. [25] Bios study group Italy	Retrospective, observational, non randomized	Non-union various sites	105	7	89
Zimmermann et al. [32]	Retrospective, observational, non randomized	Non-union various sites	23	7	92
Zimmermann et al. [33, 34]	Prospective, matched pairs, controlled trial	Non-union tibiashaft	108	7	89 sign higher
Ristiniemi et al. [23]	Prospective, controlled trial	Pilon fractures	40	7	Sign faster
Giannoudis et al. [11]	Retrospective, observational, non randomized	Non-union pelvic girdle	9	7	89
Zimmermann Moghaddam et al. (2007)	Retrospective, observational, non randomized	Non-union various sites	172	7	79

Stem-Cell Therapy

Several investigators have focussed their attention on a subset of autologous non-hematopoietic stem/progenitor cells contained in the adult bone marrow stroma, referred to as stromal stem-cells (SSC), as the appropriate cells to be transplanted [4, 20–22, 27]. The use of autologous cells is facilitated by less stringent ethical and regulatory issues and does not require the patient to be immunologically suppressed. In pre-clinical and clinical protocols of critical defects in which SSC are employed, two approaches are mainly used: in the first, SSC are derived from bone marrow and directly introduced at the lesion site, in the second, SSC are derived from several sites and are expanded ex vivo before being implanted. Both approaches, equally correct in principle, will have to demonstrate, with definitive evidence of their efficacy, their capability of solving a critical clinical problem such as non-union.

Overall there are only a few clinical studies where experience with the application of stem cells in the treatment of non-unions is reported. Most of these are from Hernigou. He investigated the relationship between number of injected cells to the healing rate [14–16].

He aspirated marrow from both anterior iliac crests, concentrated on a cell separator, and then injected into sixty non-infected atrophic non-unions of the tibia. Bone union was obtained in fifty-three patients, and the bone marrow that had been injected into the non-unions of those patients contained >1,500 progenitors/cm^3 and an average total of 54,962 ± 17,431 progenitors. There was a positive correlation between the volume of mineralized callus at 4 months and the number ($p = 0.04$) and concentration ($p = 0.01$) of fibroblast colony-forming units in the graft. There was a negative correlation between the time needed to obtain union and the concentration of fibroblast colony-forming units in the graft ($p = 0.04$).

Percutaneous autologous bone-marrow grafting seems to be an effective and safe method for the treatment of an atrophic tibial diaphyseal non-union. However, its efficacy appears to be related to the number of progenitors in the graft, and the number of progenitors available in bone marrow aspirated from the iliac crest appears to be less than optimal in the absence of concentration [1].

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