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Review article

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Modern methods of medication and local therapy for delayed fracture consolidation (literature review)

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Abstract

Introduction Management of post-traumatic disorders of bone regeneration continues to be a substantial clinical challenge in orthopaedic trauma. These include refracture, nonunion, delayed consolidation. **The purpose** is to explore modern methods of treatment of delayed fracture consolidation. **Methods** The literature search was produced via open access electronic databases of scientific literature PubMed and eLIBRARY. Search depth was 10 years. **Results** The article presents methods of medication and local therapy for delayed fracture consolidation. The effectiveness of the use of the ossein-hydroxyapatite complex and vitamin D is reported in patients with normalized healing time of a long bone fracture. The findings showed that bisphophonates, denosumab and strontium ranelate can reduce the risk of fractures with no adverse effect on bone healing. There is controversy on the effect of Teriparatide improving fracture healing. This review will envisage the current clinical trials on bone healing augmentation based on bone grafts, bone substitutes, synthetic growth factors, cell therapy and PRP therapy. Local use of bisphosphonates administered either alone or in combination with other agents is of great interest. Bisphosphonates (etidronate) locally applied in combination with lanthanide ions and calcium for animal fractures demonstrated a positive effect on the reparative process. **Conclusion** The applicability of medication and local therapy is very high in the treatment of patients with delayed fracture consolidation. Despite numerous studies many questions remain unresolved, and there is a need for the investigations. The local use of bisphosphonates was shown to be promising in the management of delayed fracture consolidation.

Keywords: fracture, delayed consolidation, reparative osteogenesis, stimulation, local factors, bisphosphonate, teriparatide

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INTRODUCTION

Management of post-traumatic disorders of bone regeneration continues to be a substantial clinical challenge in orthopaedic trauma. These include refracture, nonunion, delayed consolidation. With steady rise in trauma cases, there is increased rate of nonunions following fractures repair, poor long-term results even in specialized trauma hospitals, persistent disability among the population. Delayed consolidation occurs in 5–12 % of cases, and the incidence of nonunions in patients with bone fractures is reported to be 2–3 % of cases in relation to the total number of bone fractures [1]. Impaired reparative regeneration are multifactorial. Fracture consolidation is associated with general (age, osteoporosis, metabolic disorders, chronic limb ischemia) [2, 3] and local factors (extensive damage, inadequate reduction and fixation, infected injury).

MATERIAL AND METHODS

The literature search was produced via open access electronic databases of medical and biological publications PubMed and the scientific electronic library Elibrary between 2010 and 2020.

RESULTS

Both conservative and operative methods are used to correct delayed reparative osteogenesis [4]. Conservative management includes medication and physiotherapy. Effects of drugs on fracture healing, regenerate formation at various stages of the process are most debatable.

Experimental data suggest that calcium and vitamin D deficiency can exacerbate post-traumatic bone loss. Results of the clinical research indicate the need for supplemental calcium and vitamin D after a fracture, in osteoporotic patients, in particular [5, 6]. Basic therapy as the basis of conservative treatment of fractures is recommended by the Russian Federal Clinical Guidelines "Pathological fractures complicating osteoporosis" [7]. Daily administration of calcium preparations (with meals and/or as a drug) in combination with colecalciferol/alfacalcidol is recommended from the first days after the fracture of different localization [4]. The ossein-hydroxyapatite complex (OHC) as a calcium preparation in the form of hydroxyapatite is recommended in the first year after the fracture.

Calcium ionization in this case occurs smoothly. Unlike conventional calcium salts, OHC contains ossein, represented by collagen, osteocalcin and growth factors: TGF-b (transforming growth factor beta), IGF-I (insulin-like growth factor-1), IGF-II (insulin-like growth factor-2). The presence of growth factors contributes to the proliferation and stimulation of fibroblasts, chondrocytes and osteoblasts, collagen is responsible for the creation of a reticulofibrous matrix, while hydroxyapatite is responsible for ossification and mineralization at the fracture site and normalization of the callus formation [4]. Clinical trials were reviewed to assess the relationship between the ossein-hydroxyapatite complex and calcium carbonate and bone loss [8, 9], and the formation of a callus in the experiment. The ossein-hydroxyapatite complex was significantly more effective than calcium carbonate in women with senile osteoporosis, facilitating bones fracture healing in osteoporosis or osteopenia, patients with metabolic bone disorders (delayed consolidation after surgical treatment of nonunions complicated by regional osteoporosis). The length of healing of the femoral nonunions reduced by an average of 34.3 % as compared to the control group ($p < 0.05$) [7]. There is an evidence that bisphosphonates reduce the risk of fractures [10], and there is controversy on the specific effect of the drug on regeneration and post-traumatic bone remodeling [4]. A canine study showed that treatment with alendronate increases the volume of regenerate bone and has neither a negative nor beneficial effect on fracture healing, strength qualities and bone mineralization. However, alendronate interefered with fracture healing in rats with osteoporosis. The authors revealed a decrease in the volume of the regenerate, and poor quality regenerate was seen due to formation of coarse fibrous bone tissue at the defect site [11].

Treatment with zoledronic acid in rats with simulated femoral fracture facilitated active reparative osteogenesis with extensive extracortical subperiosteal layers formed increasing bone area and the strength characteristics with no remodeling detected at the end of the investigation. The slow regenerate remodeling was also reported by other authors who conducted animal studies [12, 13].

Similar results were observed in clinical practice [4, 11]. Alendronate therapy did not slow down fracture consolidation in osteoporotic patients who suffered a skeletal fracture. The results of the HORIZON-RFT study showed that zoledronic acid had no clinically evident effect on a low-trauma hip fracture healing, even when the drug was infused in the immediate postoperative period [11, 14]. Bisphosphonates administered early after proximal humerus fractures were reported to increase the risk of nonunion [7]. The effect of bisphosphonates on the consolidation of the broken distal metaepiphysis of the radius also remained unclear [15]. There are publications reporting such complications with bisphosphonates administered for atrial fibrillation, atypical femoral fracture, jaw necrosis, esophageal cancer [16]. However, no clear causal relationship of the complications with bisphosphonates has not been established [17, 18]. Denosumab is used as a first-line drug for hip fractures in osteoporotic cases to provide a greater increase in BMD than bisphosphonates [19–21] including increased cortical bone mass and reduced porosity. A comparative study on denosumab and zoledronic acid [22] showed significantly greater increase in BMD in the spine, femoral neck, radius due to denosumab. The FREEDOM study [7] showed absence of the negative effect on the consolidation of extravertebral fractures and hip fractures. Denosumab demonstrated clinical safety and effectiveness in other studies.

Strontium ranelate is a drug with a dual effect to simultaneously stimulate the synthesis of bone tissue and suppress the resorption. Strontium ranelate can significantly increase the strength of the bone callus having a beneficial effect on the microarchitectonics of the callosity increasing the ratio between the volume of bone trabeculae and the total volume of bone tissue formed in experimental laboratory rats [23]. Teriparatide and strontium ranelate affecting fracture healing in ovariectomized (OVX) rats when provided for the first time after the occurrence of an osteoporotic fracture was investigated in other series that combined the model of an OVX rat with a closed diaphyseal fracture [24, 25]. Although both treatments enhanced bone and tissue volume within the callus callus in strontium ranelate-treated animals was more resistant to torsion compared with control rats. A significant increase in osteoblasts and a significant decrease in osteoclasts was seen in experimental 45 rats receiving ibandronate and strontium compared to controls [26]. Subjects in both groups had significantly greater cortical bone thickness and trabecular area than controls. Animals receiving strontium had significantly more osteoblasts and a greater cortical thickness than animals of the ibandronate group. Effect of strontium ranelate therapy in combination with/without calcium preparation and vitamin D3 was investigated in a prospective study of 47 patients with hip fractures and systemic osteoporosis [27]. Pharmacological treatment of systemic osteoporosis showed no effect on the rate of fractures healing at this localization [23].

Teriparatide improves bone strength by stimulating the formation of new bone [28]. There is controversy in the literature on its effect on fracture healing. The drug can improve the consolidation of vertebral fractures and prevent progression of compression [4, 29].

Intermittent administration of teriparatide was shown to improve the formation of callus, mineral content and bone density, the mechanical strength of the callus in rat models. Teriparatide accelerated the natural fracture consolidation in monkeys with femoral osteotomy. There is controversy on this drug in clinical studies [4]. Clinical trials involving patients with femoral neck fractures [30] and teriparatide use showed no pain relief, no reduced risk of reoperations, no radiological changes in the timing of fracture healing at 12 months compared to placebo. However, a randomized multicenter study explored the effects of teriparatide in comparison with risedronate on recovery after pertrochanteric hip fractures, and teriparatide was associated with less pain and a shorter time to fracture-recovery outcomes compared with risedronate. Radiographic healing was not significantly different in the two groups [31]. A significantly shorter time-to-union was found in patients with osteoporotic intertrochanteric fractures who postfracture received teriparatide as well as calcium and vitamin D [7, 32].

Teriparatide [33] administered immediately after the proximal humerus fracture did not shorten the healing period. A significantly shorter time-to-union was found in teriparatide-treated postmenopausal women aged 45 to 85 years with a fracture of the distal metaepiphysis of the radius included in a comparative placebo-controlled study [4]. Local factors can be added to medication use to stimulate reparative osteogenesis. These factors can be classified into osteogenic, osteoconductive, osteoinductive according to biological mechanisms. An autologous bone graft possesses biologic advantages as a result of its excellent combination of osteogenic, osteoinductive, and osteoconductive properties [34]. The advantages of autograft include cost effectiveness with no risk of immunologic response and transmission of viral and bacterial disease. The disadvantages are the limited amount of available graft, insufficient structural support, pain and morbidity at the donor site. Allogeneic bone grafts (allografts) are available in a variety of formulations, cortical, cancellous, osteochondral and whole bone segment. The main disadvantage of the allograft is the loss of osteogenic potential due to the lack of donor cells.

Demineralized Bone Matrix (DBM) is a highly processed allograft that contains less than 5 % calcified cellular substance with collagens, non-collagen proteins and growth factors being preserved. DBM with lower structural and mechanical integrity than autologous bone graft, is mainly used to repair bone defects. The literature presents good results with the DMB used to repair long bone fractures [35]. However, the clinical level of evidence supporting the use of DBM in trauma and orthopaedic surgery is limited and mainly includes low-quality and retrospective cases, and the final estimates are very low [36]. Calcium sulfate, ceramics and calcium phosphate based cements, bioactive glass or their combinations are the most common synthetic bone substitutes with similar mechanical characteristics aimed at imitating osteoconductive properties of a bone graft and are mainly used for large segmental defects [37].

Synthetic growth factors include bone morphogenetic proteins (BMP), fibroblast growth factors (FGF), vascular endothelial growth factor (VEGF), platelet growth factor (PDGF) and insulin-like growth factor (IGF). The family of bone morphogenetic proteins (BMP), mainly BMP-2 and BMP-7, has found wide applications in the field of orthopaedics [38]. Several clinical studies showed that BMP-2 and BMP-7 can reduce the consolidation time after surgical treatment of tibial fractures and reduce the risk of new fractures. The BMP used for fracture repair appeared to be a favorable alternative to autologous bone grafting. The use of BMP-2 resulted in the same consolidation rates (75–89 %) as in bone autografts [39]. Contradictory results were published in other series. H.T. Aro et al. suggested that the healing of open tibial fractures treated with reamed intramedullary nail fixation was not significantly accelerated by the addition of an absorbable collagen sponge containing rhBMP-2 [40]. T. Lyon et al. demonstrated that the time to complete consolidation did not significantly decrease when using 2.0 mg/ml rhBMP-2/CPM compared with intramedullary osteosynthesis alone in 180 patients with closed tibial fractures [41]. Recombinant BMP-7 was studied in 122 patients with tibial nonunions. Although the authors concluded that BMP-7 is a safe and effective treatment for tibial fractures, the FDA did not authorize the use of BMP-7 because there was no improvement compared to autograft.

Fibroblast growth factors (FGF) are secreted by monocytes, mesenchymal stem cells, osteoblasts and chondrocytes at early stages of fracture healing throughout the consolidation process. H. Kawaguchi et al. [42] reported 70 patients with tibial fractures that healed in an accelerated manner and a higher frequency of fracture union in rhFGF treated groups compared to those treated with hydrogel alone. Kopylov V.A. et al. reported Bacillussubtilis 804 metabolites containing fibroblast growth factor having a stimulating effect on reparative osteogenesis and accelerating fracture consolidation in 56 experimental rats [43]. Platelet-Derived Growth Factor (PDGF) is a signaling molecule that is secreted by degranulating platelets at early stages of fracture healing due to its important role in chemotaxis. Although the use of rhPDGF has been approved by the FDA for ankle arthrodesis [44], there are currently no PDGF agents specifically approved for

use in fracture consolidation [37]. Vascular endothelial growth factor was shown to have an osteoinductive function. However, all available studies have been performed only on various animals [45]. The results of experimental and clinical studies indicate a positive effect of mesenchymal stem cell (MSCs) transplantation on reparative process. The volume of newly formed bone tissue, the pool of osteoblasts increase due to the osteogenic differentiation and the time for restoring bone integrity decreases [46]. The advantages of using MSCs are the minimally invasive procedure and the possibility of increasing the amount during cultivation.

The difficulty with MSCs locally injected into an open wound is that the cells are poorly retained in the defect zone. The use of matrices saturated with bone marrow suspension is one of the solutions to the problem. There is a wide range of materials used as a substrate, beta-tricalcium phosphate (β-TCF), mineralized sponge matrix, various titanium coated metals among them.

M. Jäger et al. [47] reported MSCs with collagen sponge or hydroxyapatite substrates used in the surgical treatment of patients with a fracture. Bone consolidation was radiologically confirmed in all patients at 6 months. A reduction in the formation of bone tissue at the fracture site was noted with use of hydroxyapatite as a matrix compared with the use of a collagen sponge (6.8 vs. 13.6 weeks). Complete bone recovery in these groups was recorded after 17.3 and 22.4 weeks, respectively.

PRP therapy with introduction of autologous platelet-rich blood plasma into the fracture zone is one of the well-known technologies of local stimulation of reparative osteogenesis [48]. The use of PRP in the treatment of 94 nonunions of long bones resulted in bone consolidation in 87 % of cases at 4 months [49]. Percutaneous PRP application significantly affected union rate in the treatment of oligotrophic nonunions of tibia and femur in 29 patients after intramedullary nailing of long bone fractures [50]. There are also uncertanties. In 2012 U. Sheth et al. conducted a systematic review and meta-analysis to determine the efficacy of autologous blood concentrates in decreasing pain and improving healing and function in patients with orthopaedic bone and soft-tissue injuries [51] and concluded that PRP does not offer advantages over standard treatment. There is no reliable clinical evidence to date for the use of platelet-rich plasma for bone tissue regeneration.

Local application of bisphosphonates in isolation and in combination with other components is of great interest [52]. Bisphosphonates are thought to indirectly effect bone formation increasing balance by inhibiting its resorption. However, there are studies showing that this may not be true. Morphological data on the main structural unit suggest a possible increase in the formation of a multicellular bone unit, implying that there may be some stimulating effect on its formation. Bisphosphonates *in vitro* were shown to increase the proliferation of osteoblasts and cartilage cells, biosynthesis of collagen and osteocalcin by bone cells. An increase in osteogenesis around implants was shown with the local use of bisphosphonate solution in experimental animals, and an increase in osseointegration at the implant-bone interface exceeded a similar phenomenon with the systemic use of bisphosphonates. Used as a local treatment, a higher local dose of bisphosphonate can be achieved without systemic exposure in cement joint replacement. However, there were changes in cement characteristics with reduced fatigue strength, and therefore the idea had to be abandoned.

The predominant use of cement-free constructs, the impossibility of using bisphosphonates in combination with bone cement and insufficient efficiency with bisphosphonates combined with hydroxyapatite coating initiated development of solutions of bisphosphonates for local use [53]. However, it was found that bisphosphonates as a solution were unable to persist at the injury site for a long time [54]. A non-penetrating tibial defect was simulated in 36 rabbit to explore reparative osteogenesis [55]. Ethidronate (first–generation bisphosphonate without amino group content was injected into the defect site in the main group to inhibit bone resorption by induction of osteoclast apoptosis) and calcium, and no injection produced in the comparison group in order to retain the components of lanthanides. Lanthanides are rare earth metals and are effective catalysts for the hydrolytic cleavage of phosphate-ether bonds [56]. Lanthanide-containing biocomposition coatings can improve the trophics of the bone-implant border, accelerate osseointegration and prevent inflammatory complications due to antiplatelet activity. Lanthanides can have an antimicrobial effect, increase the phagocytic activity of leukocytes with resultant rejection of necrotic tissues, facilitate cell proliferation and rapid healing of the wound surface [57]. The findings of this study showed that the dosed use of a ethidronate containing drug, lanthanide ions and calcium can be effective at early stages of healing of small bone defects, and a significant pronounced difference in bone density was revealed at early stages of the reparative regeneration. The complex effect of the drug was associated with a decrease in the intensity of inflammation; accelerated repair and osteogenesis that was direct in the majority of cases. The ability of a preparation containing ethidronates of lanthanide ions and calcium to significantly stimulate osteoblasts activity without suppression of osteoclast activity *in vitro* was reported [58].

Another study on 45 rats [59] aimed at assessing changes in bone density at the fracture site repaired with IM nailing and local use of ethidronates based components, lanthanide ions and calcium demonstrated that the paraossal use of ethidronates based components, lanthanide ions and calcium was accompanied by formation of the cortical bone at the site of osteotomy with the highest density parameters that normalized faster than in the group with the introduction of ethidronates based components and calcium without lanthanide ions. Morphological examination [60] exhibited the best fractures healing time with paraossal administration of ethidronate in combination with lanthanides. Hematological examinations of 75 rats [61] showed no negative effect on the rat body with components that contained lanthanide ions and ethidronate.

CONCLUSION

Despite improvement in surgical treatment of fractures and use of modern materials and technologies delayed consolidation and nonunion are among the most challenging clinical complications in the repair of bone fractures. The literature review indicated relevant use of medications and local factors for bone restoration and regeneration. However, despite numerous studies many questions remain unresolved and there is a need to explore them. Local use of bisphosphonates was shown to be promising in the treatment of delayed fracture consolidation.

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