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Stimulation of Osteogenesis by Direct Electric Current (Review)

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Abstract

Background. Stimulation of osteogenesis in the treatment of certain orthopedic and trauma pathologies is a necessary element to ensure the best clinical outcome. ***The purpose*** of the analytical review is to analyze the literature data in respect of evaluating the approaches and possibilities to stimulate osteogenesis using direct current. ***Methodology.*** The search for literature data was performed in the open electronic databases of scientific literature PubMed and eLIBRARY under the following keywords and their combinations: “osteogenesis”, “reparative osteogenesis”, “direct electric current”, “orthopaedics”, “traumatology”, “electric current” (in Russian as well as in English language). Results. According to some fundamental research, the stimulating effect of direct current lies is both in stimulating differentiation and proliferation of osteoblasts, and in stimulating differentiation of stem cells, mainly mesenchymal stem cells of bone marrow and adipose tissue, in the process of osteogenesis. The following stimulating technologies were developed and clinically tested to date: 1 — direct exposure of bone to the direct current; 2 — capacitive coupled stimulation; and 3 — inductive coupled (electromagnetic) stimulation. Analysis of clinical practice demonstrated that the first technology is most effective in terms of osteoreparation, but less safe than technology 2 and 3. It should be noted that there are no clear indications and modes of application for the abovementioned methods. Based on the data collected in the present analysis, technology 1 is considered by authors as the most promising. Safety of technology 1 can be enhanced by application of metal implants as electrodes in case those are planned to be used for medical reasons: wires, rods, staples, fixators, etc. Conclusion. Use of electric current to stimulate bone formation is a promising method which requires clarification in respect of indications and application modes.

Keywords: osteogenesis, electrostimulation, direct electric current.

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Introduction

Stimulation of bone formation remains a pressing issues of practical trauma and orthopaedic surgery. The need in such stimulation arises to solve the task of faster fracture healing and to accelerate bone formation in treatment of orthopaedic pathologies [1, 2]. In orthopaedics the stimulating effect is aimed at:

– improvement of bony integration of metal implants [3];

– acceleration of growth and mineralization of bone regeneration during replacement of bone defects and/or during limbs lengthening [4, 5].

In clinical use of external fixators and prostheses the additional reasons for stimulation of bone formation is the minimization of iatrogenic risks (infection of implants, contractures, muscles atrophy, etc) as well as reduction of everyday and psychological discomfort of a patient related to prolonged application of external fixator [6–8]. Based on these considerations stimulation of osteogenesis looks quite rational and necessary element in treatment of patients using external fixators to reduce treatment time. This may help reducing iatrogenic risks and have medical and economic expediency. Application of electric stimulation can be rather efficient in this respect [9].

The purpose of the analytical review is to analyze the literature data in respect of evaluating the approaches and possibilities to stimulate osteogenesis using direct current.

Strategy of literature search

The search for literature data was performed in the open electronic databases of scientific publications — PubMed and eLIBRARY — under the following keywords and their combinations: “osteogenesis”, “bone formation”, “restoration osteogenesis”, “direct electric current”, “orthopaedics”, “traumatology”, “electric current” (in Russian as well as in English languages). Search horizon was 30 years.

The authors determined inclusion and exclusion criteria to conduct analysis of evaluation of the data.

Inclusion criteria: availability of full text sources or structured abstracts indicating particular quantitative data.

Exclusion criteria: clinical cases; lecture theses; research with signs of “unoriginality” and “duplication” (similar research protocol, groups, number of patients, etc). If such publications were identified, a paper later in the publication date was chosen.

Results

In vitro evaluation of electrostimulation effects

Currently it’s known that the effect of stimulation of bone formation under direct electric current is based on the phenomenon of osteoblasts migration to the electrode acting as cathode with subsequent osteoblasts differentiation and proliferation on this electrode [10–13]. Modern research demonstrates that the stimulating effect of direct current consists not only of osteoblasts but also precursor cell stimulation. In particular, many researchers observed that direct electric current stimulates differentiation of stem cell, mainly mesenchymal stem cells of bone marrow and adipose tissue in the process of osteogenesis. Summary data of mentioned research are given in table.

So, available fundamental studies convincingly proved systemic character of stimulating effect of direct electric current on cellular elements of the bone. Taking into account that this effect was demonstrated rather long ago, by now a certain experience of electrostimulation in clinical and experimental practice was accumulated by now.

Table

Publications describing proven stimulation effect of stem cells differentiation for bone formation under direct electric current

Source	Cells	Current parameters	Stimulation mode	Comments
Eischen-Loges M. et al [14]	MSC BM (rat)	100 mV	1 hour during 7 days	No effect was observed at 1 hour mode during 3 days
Wang X. et al [15]	MSC BM (rat)	200 mV	4 hours once	Stimulation effect on positive electrode
Mobini S. et al [16]	MSC BM (rat)	100 mV	1 hour during 7 days	Cells lysis observed at 200mV mode
Mobini S. et al [16]	MSC AT (rat)	100 mV	1 hour during 14 days	–
Hu W.W. et al [17]	MSC BM (rat)	35 mV	4 hours once	–
Zhang J. et al [18]	MSC AT (human)	200 μA	4 hours during 21 days	–

MSC — mesenchymal stem cells; BM — bone marrow; AT — adipose tissue.

In vivo evaluation of electrostimulation effects

Three stimulation techniques were developed and clinically tested [19, 20] based on known stimulating effect of direct electric current on bone formation on the cathode.

Technique 1 — direct exposure of bone to the direct current. The method stipulates implantation of cathode into the bone fracture area. Anode is placed on the skin above the fracture site. Applied current was from 5 to 100 μA.

Technique 2 — capacitive coupled stimulation. The present method is non-invasive. Electrodes are placed on the skin above fracture area in such a pattern that the fracture section is located between the electrodes. The external supply is attached to the electrodes inducing electric field at the application site. Current parameters: 1-10 V at frequency of 20-200 Hz resulting in creation of electric fields from 1 to 100 mV/cm at the area of bone fracture.

Technique 3 — inductive coupled (electromagnetic) stimulation. Electromagnetic coil attached to the external power source is placed on the skin over fracture site. The coil generates magnetic field which induces electric field in the fracture area.

Various devices for clinical application of electric current for stimulation of osteogenesis are currently developed, experimentally tested and registered. The list of devices and scope of their application are described in detail in the review of M. Griffin and A. Bayat [19].

The majority of authors give a positive feedback on clinical application of mentioned techniques, however, acknowledge that the key factor preventing wide introduction in the practice the absence of clear and justified indications [20–23]. Other challenges arise in standardization and unification of stimulation terms: selection of current parameters, time and periodicity of effect, exposure start time after injuries or surgeries [24]. Abovementioned data of in vitro research where cellular effect is obtained at various modes of electrostimulation also indicate complexity in choosing application terms.

When evaluating the abovementioned techniques separately, the literature demonstrates that non-invasive character of techniques 2 and 3 ensures their undoubted advantage for clinical practice due to safety [25]. However, these techniques have a disadvantage, namely absence of targeted impact on the bone while the exposure goes through periosteal tissues. This fact significantly reduces the efficiency of techniques 2 and 3 and makes their application insufficiently justified for wide clinical practice [26, 27].

The advantage of the 1st technique for stimulation (cathode stimulation at the site of injury) is its efficiency which has been proven in a series of experimental works [28–30]. At the same time there is data available demonstrating that application of this technique is not always efficient, in particular for healing of skull bones defects [31].

Clinical experience available by now in application of technique 1 to stimulate bone formation was positive in cases for acceleration of delayed healing, stimulation of ankylosis formation, and stimulation of bone regeneration in cyst area after grafting [19, 20, 32, 33, 34, 35]. In particular, literature revealed that consolidation for delayed healing after application of direct electric current is observed in 62,5-92,9% of cases. At the same time, results of controlled randomized studies report successfully spinal fusion in patients undergoing stimulation by direct electric current in the range of 91,5-95% while in patients without electrostimulation positive outcomes were observed in 75-85% of cases [19].

Nevertheless, invasive character of this technique seriously limits it's clinical application, including due to the risk of infection of implanted electrode [36]. Besides, the use of direct electrostimulation for osteogenesis can be accompanied by intoxication of the tissues by corrosion particles of the implants [37].

So, application of direct current stimulation is more efficient for ostegenesis than use of indirect stimulation. The latter, however, are safer in clinical application in terms of invasive features and complications rate. Even so, many authors indicate that electrostimulation techniques should be used only as additional effect in treatment of orthopaedic and trauma pathologies and strictly for medical indications [9, 19, 33].

The authors of the present study consider that technique 1 is the most efficient for bone formation and its safety parameters can be enhanced by application of metal implants as electrodes in case those are planned to be used for medical indications: wires, rods, staples, fixators, etc.

Certain research in this respect was already undertaken. In particular, demonstrating possibilities of electrostimulation for osteogenesis along metal dental implants to improve their osteointegration [38, 39] and electrostimulation along intramedullary pins to accelerate recovery of injured bones [40-42].

All studies illustrated that use of implanted devices as cathodes can be a rather promising option for stimulation of bone formation (at the bone-implant interface). It's noted that a significant advantage of this approach is reduction of infecting implants used as electrodes due to antimicrobial effect created by electric current [43, 44].

Thus, the available studies indicate that application of implants as cathodes for electrostimulation potentially possesses efficiency no less than special devices for direct electrostimulation. This also enhances safety of the technique due to no need for additional invasion for cathode implantation and reduces risk of infecting of metal implants.

It's worth mentioning separate options for electrostimulation of bone formation during application of external fixators including Ilizarov apparatus. Undoubtedly, the design of external fixator itself allows to create current in the operated segment using transosseous components as electrodes (pins, screws) [45]. However, achievement of local stimulating effect can be difficult while implanted pins fixing bone fragments are placed away from bone regenerate. Partially this issues can be solved by using a special pin or screw partially of fully covered by insulated material to fix fragments. Modern technologies of application of polymers allow producing such device without significant rise in the cost of manufacturing.

Experimental works available by now demonstrate positive osteogenic effect of electrostimulation using pins for Ilizarov apparatus as electrodes, in particular on the model of distraction osteogenesis [46–49]. In all cases the stimulating effect was achieved by earlier mineralization of distraction regenerate at the stage of fixation, that why last days of distraction and first days of fixation are considered optimal terms for electrostimulation.

It's believed that reported positive outcome of stimulation in distraction osteogenesis has a cumulative character, namely, adding direct electric current effect of the regenerate (first of all through periosteal tissues) and capacitive coupled electromagnetic stimulation achieved during current flow along closed "Ilizarov fixator — limb" system. Therefore, available cases demonstrate promising application of electrostimulation for bone formation through pins of external fixators used in trauma and in orthopaedic surgery.

The analysis of literature data allows to conclude that various approaches and technical solutions were fundamentally justified and developed by now for electrostimulation of bone formation. However wide introduction of these techniques into the clinical practice is complicated due to absence of clear indications and application modes for methods of electrical effects as well as due to lack of clinically proven information on efficiency and acceptable safety. So, it's difficult to perform comparative evaluation of efficiency of electrostimulation techniques described in this paper. However, targeted local pattern of stimulation specified by technique 1, the capacity to reduce its invasion by using implants as electrodes for treatment of trauma and orthopaedic pathologies (pins, nails, screws, etc) makes this approach in the authors' opinion the most promising for further clinical use. Moreover, for the implementation of this option there is already a fundamental basis (proved effect of cathode stimulation) and a series of encouraging experimental observations.

Use of electric current for stimulation of bone formation is a promising method which, though, requires clarification of indications and application modes.

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Authors' contribution

Ovchinnikov E.N. — analysis and interpretation of the results, writting of the paper.

Stogov M.V. — selection of publications for review, interpretation of results.

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