

Accelerating the Bone Healing Process by the Intervention of the Platelet Growth Factors Impregnated in Collagen

An experimental and theoretical mathematical model

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A bone defect with standard dimensions and localization is produced. Inside this defect a polymer (collagen sponge) impregnated with growing factors, i. e. bone morphogenetic protein – BMP, is introduced. For the witness lot, the same defect is produced, in which the same polymer is introduced, but without any growing factors. It is found that the growing factor not only remains at the initial site, but also has effect on the bone regeneration process. A mathematical model is constructed using a field theory of multifractal type based on the spontaneous symmetry breaking mechanism to exploit such dynamics in biostructures. This mechanism contains all the informational “ingredients”: the multivalent logic based multifractal bit, the algorithm based networks through spatial cnoidal modes of oscillation, etc. In such context, the evolution of all biostructures, through a mechanism that mimics a 3D biological printer, can become operational.

Keywords: bone, collagen, multifractal

The surgical reconstruction of the orbit represents one of the most complex fields of reconstruction. It imposes a multidisciplinary team approach: plastic surgery, ophthalmology and neurosurgery. The main cause of the orbital defects is represented by the orbital trauma, followed by the tumoral and malformative pathology.

Often difficult to be archived, the reconstructive treatment of the orbital defects may have some immediate and long time complication, that limit even more the obtaining of an optimal result. One of the most often complication is represented by the lack of normal bone consolidation leading to major orbital architecture disruption. This has an enormous impact in the positioning of the eye globe and implicitly on the visual function. The rate of this complication is greater with the number of the facial segments involved.

The main causes of bone healing failures are: lack of the correct bone fragments alignment, inadequate hemostasis, infections, insufficient immobilisation of the fracture site, resorption of the bone grafts used for reconstruction of the bone defects, osteosynthesis materials protrusion, delayed surgical treatment, large soft tissue defects [1].

Bone defects larger than 2 mm impose covering of this defects and fracture stabilisation with osteosynthesis materials. The most used bone grafts materials are autologous bone, bone substitutes like hydroxyapatite, methyl methacrylate, demineralised bone. The use of this substitutes base on the principles of osteoinduction and osteoconduction in bone regeneration process.

The modern techniques of tissue engineering have developed new methods to stimulate the osteogenesis process with the participation of the growth factors.

One of the most used biomaterials are those based on collagen because the human or animal body consider it as one of its constituents and not as an unknown material, having excellent biocompatibility, biodegradability, as it is extracted from skin, tendons, cornea from different animals (bovine, porcine, ovine, bird, fish).

Due to its properties collagen can be used in burn/wound dressings, bone filling materials, and also in tissue engineering including skin replacement and bone substitutes [2].

Although up to now have been identified 29 different types of collagen, the type I, of bovine origin, is the most studied and used in applications. It contains 20 amino acids, in a conformational structure of triple helix (Fig. 1).

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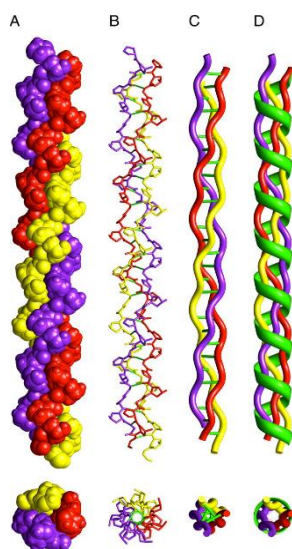


Fig. 1. Different representations of a collagen triple helix

In Fig. 1, the three polypeptide chains are shown in purple, red and yellow, in side view and top view of the same representations: i) space-filling diagram (A), ii) stick diagram, showing hydrogen bonds as green sticks connecting the chains (B), iii) ribbon diagram showing the ladder of hydrogen bonds perpendicular to the helix axis (C), iv) ribbon diagram including the left-handed superhelix (green), which describes mathematically the collagen triple helix as a continuous helix of repeating units across the three individual strands (D) [3].

Collagen stability is determined by the presence of hydroxyproline, a common non-proteinogenic amino acid, that permit the sharp twisting of the collagen helix.

Biomaterials based on collagen can be obtained in forms of hydrogels, membranes, matrices (spongy), composites, through cross-linking, free drying, lyophilization, electrospinning or their combinations, at temperatures lower than 30°C, in order to maintain the triple helix structural conformation.

Collagen gels, most commonly used as carrier systems, are tridimensional networks of collagen chains obtained by physical (drying by heating or exposure at UV, gamma or beta irradiations) or chemical (reaction with aldehydes, carboimides, polyphenolic compounds) cross-linking of gels, that determines the formation of ionic or covalent bonds between molecules, the resulting hydrogels having properties controllable and superior to the gels from which they were obtained. Among their properties very important for pharmaceutical applications distinguish their capacity of hydration through soaking or swelling with water and biological fluids, maintain the shape, due to isotropic soaking.

These gels are impregnated with growing factors as: PDGF α (platelet-derived growth factor α), PDGF b (platelet-derived growth factor b), TGF (transforming growth factor), VEGF (vascular endothelial growth factor) epithelial growth factor [4]. Clinical studies primarily directed to the maxillofacial sphere indicates the ability of PDGF to induce bone maturation, stimulation of macrophage activation, mitogenesis and angiogenesis, while TGF activates the isoblastic functions (mitogenesis of collagen). BMP (bone morphogenetic protein) is a subgroup of TGF and has an established role in vitro and in vivo, stimulating stem cell differentiation in osteoblasts and bone tissue formation by modulation of bone matrix synthesis. TGF b reduces bone resorption by stimulating osteoclast apoptosis. The bone maturation process is then induced by the BMP that is constituted in the bone matrix by the resorption of the osteoclasts. It will induce the differentiation of stem cells from neighbouring tissues into osteoblasts.

The bone repair process is based on three principles: osteoinduction, osteoconduction and osteogenesis [5, 6].

Osteoinduction is the process by which the mesenchymal stem cells that most commonly come from the bone marrow, adjacent muscles or neovessels, under the influence of BMP will differentiate into osteoblasts.

Osteoconduction is the ability of different structures to provide a matrix at which the new bone tissue will form. Most often this is represented by autologous bone tissue, calcified cartilage and collagen.

Osteogenesis is the process of bone matrix synthesis.

Tissue engineering studies have shown that the isolate dose of growth factors in the treatment of facial mass fractures is not effective, largely because of their short life span.

Most commonly used as carrier systems today are gels obtained by mixing platelet plasma concentrates (PRPs) with thrombin (so-called platelet gels), methyl methacrylate, hydroxyapatite, calcium triphosphate [7-9]. All these systems appear to be able to act as temporary matrix for neovascularization and bone growth processes. But none of these systems proved to be effective for each of the three stages of bone regeneration. Especially the process of osteoinduction seems to be the most affected [10-12].

It has also been found that platelets density in the carrier system is overwhelming important in stimulating the bone repair process. Although most studies indicate a 5- to 10-fold higher platelet density at the PRP level than serum levels, the ratio in which platelet concentrate to the carrier system should be used is unknown [13, 14].

The present study aims to study the experimental model of the action way of the platelet growth factors in the process of bone healing of the post-traumatic defects of the orbit.

Experimental part

Materials and methods

To describe the experimental model we use rabbits with a weight between 1800 and 2100 g. In total, a number of 10 rabbits were operated, divided into two lots, the control lot and the growth factors lot, each of 5 rabbits.

All animals were operated in compliance with the provisions of Law no.205/2004 on the National and Medical Research Guidelines for Animal Welfare as well as with the intentional legislation in the field.

Surgical interventions were made under general anesthesia with Somnopenthy 10.5ml/kgc, provided by lower limb intramuscular injection.

After anesthesia is installed, the animal is placed in dorsal decubitus. 4 ml of blood was withdrawn from the femoral artery and inserted into the special drains from the Plasma Lift separation kits. The tubes are centrifuged at 3500 rpm for 9 minutes. After centrifugation the separator gel is positioned between the platelets and the plasma (above) and the blood/white blood cells (underneath) (Fig. 2). The platelet film adhering to the surface of the separating gel is aspirated with a fine needle along with 0.5ml of plasma. The aspiration is absorbed on small fragments of collagen sponge (1-2 mm long) (Fig. 3). This operatory step is not done for the rabbits in the control group.

Within the control group, the collagen sponges are impregnated with physiological serum.



Fig. 2. The platelet film separated to the gel



Fig. 3. Colagen sponge with PRP

After harvesting the blood, the rabbit is positioned in the ventral decubitus with the head resting on a textile support (operator field). For ease of intervention, the rabbit is raked with an electric, veterinary razor, from the lower eyelid to the nape.

1 to 1.5 ml of anesthetic and vasoconstrictor solution (lidocaine 1% + adrenaline 1:100000) is injected at the lower orbital rim and 1-1.5 cm lower.

An incision of approximately 2 cm is performed along the inferior and medial orbital rim down to the periosteum (Fig. 4). Using 2 retractors, the wounds margins are retracted and the periosteum of the lower and middle orbital rim is removed up to 3-4 mm below the infra orbital foramen. Also, the 4 mm of the orbital floor periosteum is removed. With a 4 mm osteotome and a hammer, three osteotomies are performed which, together with the orbital rim, separate a quadrilateral fragment from the anterior wall of the maxillary sinus. Osteotomies are made superior to the infraorbital foramen, in order to prevent damaging the infra orbital bundle (Fig. 5). The bone fragment is extracted and further segmented, after which it is repositioned in the defects on that it only partially covers (about 50%) the bone defect.

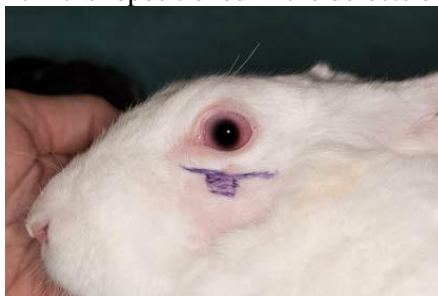


Fig. 4. Preoperatory drawing



Fig. 5. Bone defect

In the rest of the defect, sponges impregnated with platelet aspiration (in the case of growth factors group) and saline (in the case of the control group) are introduced (Fig. 6).



Fig. 6. The platelet impregnated sponge at the bone defect site

The periosteum over the remaining defect and the skin are sutured.

After the surgery the rabbits are all owed to feed and mobilize without restriction, being housed one in a cage. Each animal is examined daily.

At 21 days after the initial surgery, the fracture focal is examined. The rabbits are anesthetized under the same conditions and the initial operative wound is reopened. Using a minipunch (1.2 mm diameter), a tissue fragment from the former bone defect is collected to perform the anatomopathological examination). The periosteal and cutaneous wound are sutured.

In the same manner, the fractures are reevaluated at 3 months and one year after the initial intervention.

Results and discussions

A total of 10 rabbits were operated, divided into two lots: the control group and the growth factors group, all owing the description of the experimental model of the study of the action of the platelet growth factors at the level of the orbital fracture.

The experimental model described is simple to achieve, reproducible, the average running time being 33 minutes (between 45-20 minutes), with an extremely short learning curve.

Although no anatomopathological examinations were performed, direct examination at 21 days and 3 months of fractures demonstrated a much reduced inflammatory response at the level of the fracture focals; at 3 weeks postoperatively in the case of the group of growth factors versus the control group and a superior bone consolidation at 3 months in the control group compared to the growth factor group.

The results of the surgical interventions in the described experimental model were not evaluated at one postoperative year (the time considered necessary for the completion of the fourth stage of bone healing-bone remodeling); however, after 3 months postoperative, healing of bone defects in the batch of platelet growth factors is complete and only partially in the control group. This suggests an acceleration of the bone healing process by platelet growth factors. The rate of resorption of the collagen sponge used at the fractures it is very difficult to assess. Similarly, the rate of release of platelet growth factors at this level is difficult to influence, depending on the rate of resorption of the collagen sponge used.

The most accurate assessment of bone healing should be made by analyzing bone specimens at the electron microscope.

Theoretical mathematical model

Multifractal approach proved to be an alternative at mathematical modeling of drug release from polymeric matrices [15], such as hydrogels [16], microparticles [17, 18].

Let's admit that both from structural and functional point of view, the complex system: bone - collagen sponge - growing factors biostructure is of multifractal type. Then, its dynamics are described by continuous and non-differentiable curves, that will allow, based on the self-similarity properties of the motion curves, a holographic explication of the dynamics of the complex system in the form of "the whole reflects the part and vice versa".

Since bone regeneration can be assimilated, from a physical point of view, to a mass-generating effect, it results that a multifractal field theory with spontaneous symmetry breaking can describe such dynamics in biostructures. If we describe now the state of the complex system through the multifractal state function f , then its stationary dynamics in a multifractal field theory with spontaneous symmetry breaking is expressed by the differential equation [19-25]:

$$\partial_{\xi\xi} f = f^3 - f \quad (1)$$

where:

$$\partial_{\xi\xi} = \frac{\partial^2}{\partial \xi^2}$$

with ξ a non dimensional multifractal spatial coordinate.

Equation (1) can be also obtained from the variational principle $\delta \int L dv$ (with dv the elementary volume) applied to the multifractal Lagrangian density:

$$L = \frac{1}{2} (\partial_{\xi} f)^2 - g(f) \quad (2)$$

of multifractal potential:

$$\theta(f) = \left(\frac{f^4}{4} \right) - \left(\frac{f^2}{2} \right) \quad (3)$$

Equation (1) has solutions $f = 0, f = \pm 1$. Calculating the second derivative of θ in relation to f , it results $\theta_{ff}(0) = -1, \theta_{ff}(\pm 1) = 2 > 0$. Also it results that the solution $f_v = \pm 1$ is associated with the multifractal minimum energy. So, the considered model has a double degenerate multifractal "vacuum state". We recall that the multifractal "vacuum state" means the fundamental state of the complex system bone - collagen sponge - growing factors biostructure.

From (2) we obtain both the expression of multifractal energy

$$\varepsilon(f) = \int_{-\infty}^{+\infty} d\xi \left[\frac{1}{2} (\partial_{\xi} f)^2 + \theta(f) \right] \quad (4)$$

as well as that of the energy reported to the multifractal "vacuum state":

$$\varepsilon(f) - \varepsilon(f_0) = \int_{-\infty}^{+\infty} d\xi \left[\frac{1}{2} (\partial_{\xi} f)^2 + \frac{1}{4} (f^2 - 1)^2 \right] \quad (5)$$

Since all the terms in (5) are positive and considering the infinite integration limits, the finitude of multifractal energy implies for $\xi \rightarrow \pm\infty$

$$\partial_{\xi} f = 0, \quad \frac{1}{4} (f^2 - 1)^2 = 0 \quad (6)$$

From here it results that for $\xi \rightarrow \pm\infty$ the function $f(\xi)$ tends to its multifractal vacuum value $f_v \rightarrow \pm 1$. To find the explicit form of the solution of the equation (1), we will multiply it with $\partial_{\xi} f$. It results first:

$$\frac{1}{2} (\partial_{\xi} f)^2 = \frac{-f^2}{2} + \frac{f^4}{4} + \frac{1}{2} f_0 \quad (7)$$

or still through integration:

$$\xi - \xi^0 = \int_0^f \frac{df}{\sqrt{\frac{f^4}{2} - f^2 + f_0}} \quad (8)$$

where f_0 and ξ^0 are two integration constants. From this general solution an infinite value of multifractal energy $\varepsilon(f)$ is obtained, for an arbitrary f_0 . To obtain the finite multifractal energy solution, we will use the limit conditions $f_v = \pm 1$. From (7), it results $f_0 = 1/2$. By replacing this value of f_0 in (8), the solution $f_k(\xi)$ of the finite multifractal energy field equation (1) is:

$$f_k(\xi) = f(\xi - \xi^0) = \tanh \left[\frac{1}{\sqrt{2}} (\xi - \xi^0) \right] \quad (9)$$

This is called the multifractal kink solution. For details on the properties the classical kink solution, see the reference [26].

By combining (5) with the expression $f_v = 1$ and the expression of f_k , we will obtain the relative multifractal kink energy of vacuum:

$$\varepsilon(f_k) - \varepsilon(f_v) = \frac{2\sqrt{3}}{3} \quad (10)$$

A topological method can be applied next because the admissible number of multifractal kinks is determined by the topological properties of the group with allows invariant the equation (1). In this context, the following problems can be solved: i) the admissible number of multifractal kink solutions induced by the topological properties of the equation (1); ii) multifractal topological change.

The multifractal kink solution can be obtained as a map of a zero-dimensional sphere S^0 , taken infinitely on the double degenerate multifractal vacuum induced by the model (1). The homotopic group corresponding to this model is $\Pi_0(Z_0) = Z_2$, i.e. the model admits two solutions: the constant solution f_v and the multifractal kink solution (for details, see [27-33]).

The associated multifractal topological change is:

$$q = \frac{1}{2} \int_{-\infty}^{+\infty} j(\xi) d\xi = \frac{1}{2} \int_{-\infty}^{+\infty} \frac{df}{d\xi} d\xi = \frac{1}{2} [f(+\infty) - f(-\infty)] \quad (11)$$

The multifractal vacuum solution (in the absence of spatial gradients) and the multifractal kink solution can be characterized by the multifractal topological change $q = 0$, respectively $q = 1$ (the result is obtained by a specific normalization of f). Thus, the multifractal information bit is highlighted.

In the general case, the integral (8) with the substitutions:

$$w = \frac{f}{f_1}, k = \frac{f_1}{f_2}, f_1^2 = \frac{2k^2}{1+k^2}, f_2^2 = \frac{2}{1+k^2}, f_{1,2}^2 = 1 + (1 + 2f_0)^{1/2} \quad (12)$$

take the standard form:

$$\frac{(\xi - \xi_0)}{(1+k^2)^2} = \int_0^{w_1} \frac{dw}{[(1-w^2)(1-k^2w^2)]^{1/2}} \quad (13)$$

with

$$w_1 = f \left(\frac{1+k^2}{2k^2} \right)^{1/2} \quad (14)$$

By inverting it, the solutions class is obtained:

$$f = \left(\frac{2k^2}{1+k^2} \right) sn \left[\frac{(\xi - \xi_0)}{(1+k^2)^{1/2}}; k \right] \quad (15)$$

where sn is Jacobi's elliptic function of module k [34]. For $k \rightarrow 0$, the relation (15) can be approximated by:

$$f = \left(\frac{2k^2}{1+k^2} \right)^{1/2} \sin \left[\frac{(\xi - \xi_0)}{(1+k^2)^{1/2}} \right] \rightarrow 0 \quad (16)$$

while for $k \rightarrow 1$, with the kink solution:

$$f \rightarrow \left(\frac{2k^2}{1+k^2} \right)^{1/2} \tanh \left[\frac{(\xi - \xi_0)}{(1+k^2)^{1/2}} \right] \quad (17)$$

Since only f^2 has physical significance, it results only through the difference:

$$Q = 1 - f^2 = \frac{1-k^2}{1+k^2} + \frac{2k^2}{1+k^2} cn^2 \left[\frac{(\xi - \xi_0); k}{(1+k^2)^{1/2}} \right] \quad (18)$$

we can "control" and "direct" the potentiality of informational energy in the Onicescu sense (for details, see [35]). The fact that such a potentiality is expressed through cnoidal spatial oscillations of the biostructure and the fact that such modes can be put in correspondence with standard neural networks shows that such a biostructure can function as a 3D biological printer (for details, see [36]).

Conclusions

The experimental model described is an excellent model for the study of the mode of influencing the bone healing process by the platelet growth factors. It is a simple model, with a short learning curve, relatively inexpensive, reproducible.

Apart from analyzing the evolution of the bone healing process, the experimental model described will allow the following objectives to be achieved:

- selection of biodegradable and biocompatible polymers active at the fractures in the biological microclimate similar to the existing one at this level;
- determination of compound degradation rate and release of growth factors;
- preparation of polymeric compounds;
- in vivo testing of biocompatibility and determination of tissue tolerance;

- preparation of osteoinductive, osteoconductive and osteogenic complex systems usable in the reconstruction of bone defects of the orbit;
- determine the optimal ratio between platelet concentration and polymer volume for optimal therapeutic response;
- in vivo demonstration of the effectiveness of using the compound obtained by histopathological examinations and bone density determination in the experimental animal.

The experimental model described will allow for a better understanding of the importance of the carrier system composition over the growth factor action.

The mathematical model built can express the generation of biostructures through a mechanism that mimics a 3D biologic printer. So, the spontaneous symmetry breaking is the mechanism by which the mass can be physically generated. This mechanism contains all the informational "ingredients" necessary: the multivalent logic based on the multifractal bit, the algorithm based networks through spatial cnoidal modes of oscillation, etc.

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