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REVIEWS

BASIC PRINCIPLES FOR PREDICTIVE REGENERATIVE THERAPY

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ABSTRACT

INTRODUCTION: We can now talk about *predictive regenerative therapy* thanks to the fact that there are a series of basic principles that, if taken into account, would guarantee the results we would like to achieve. These principles include primary wound closure, good angiogenesis, barrier function for the required period of time, ensuring and maintaining the space of the bone defect and keeping the blood clot stable.

AIM: The purpose of this review article is to present a general overview of the above-listed basic principles for achieving predictable results in regenerative therapy.

MATERIALS AND METHODS: Keywords such as "regenerative therapy", "regenerative principles", "guided tissue regeneration", and "guided bone regeneration" were utilized to search Web of Science and Scopus for related scientific articles published in English up until 2024. The literature was thoroughly analyzed. After thoroughly reviewing the reference list, all papers were evaluated and examined for more relevant research.

RESULTS: The basic principles that are necessary to achieve predictable regenerative outcomes are primary wound closure, good angiogenesis, barrier function for the required period of time, securing and maintaining the bone defect area, and keeping the blood clot stable.

CONCLUSION: Both a high degree of technical proficiency and a comprehensive understanding of the fundamentals of wound healing are necessary for a successful predictive regeneration.

Keywords: *regenerative therapy, guided tissue regeneration, guided bone regeneration, regenerative principles*

INTRODUCTION

In daily practice, clinicians regularly encounter cases where it is necessary to resort to various methods of regenerative therapy. Different methods and biomaterials have been introduced to facilitate bone and soft-tissue reconstruction (1–3). Today, guided tissue regeneration (GTR) and guided bone regeneration (GBR) are considered surgical procedures of fundamental importance (4).

The guiding biological principle of these methods lies in the use of a physical barrier that inhibits the proliferation of gingival epithelial and connective tissue and thus enables slower regenerating tissues to repair the defect (5,6).

Regenerative therapy has been studied for decades. There are studies in the literature that present different clinical and radiological results. Some of these results are impressive, others not so much. Today we can talk about *predictive regenerative therapy* thanks to the fact that there are a series of basic

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principles that, if taken into account, would guarantee the results we would like to achieve (7,8).

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RESULTS AND DISCUSSION

The basic principles that are necessary to achieve predictable regenerative outcomes are primary wound closure, good angiogenesis, barrier function for the required period of time, securing and maintaining the bone defect space, and keeping the blood clot stable (Fig. 1).

Primary Wound Closure Without Tension

Wound healing can occur by primary or secondary closure.

The edges of a wound are positioned together in a nearly identical configuration to their pre-injury state during primary intension healing. Secondary intention is the term used to characterize healing that takes place when the borders of a wound cannot be closely approximated. This makes the wound heal more slowly, necessitates more collagen remodeling, and increases the likelihood of scarring (7). Primary wound closure is very often extremely difficult to achieve in regenerative therapy. However, this type of wound healing is a fundamental principle for predictive regenerative therapy, as it creates the only way to keep the defect area from being contaminated (9,10).

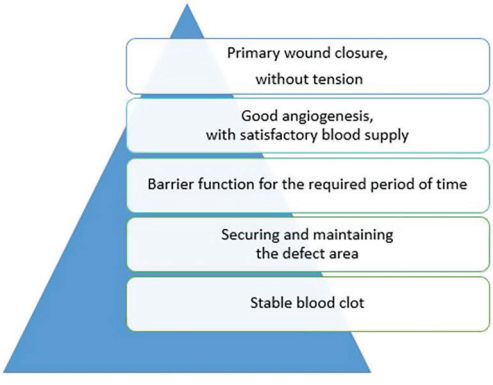


Fig. 1. Basic principles necessary to achieve predictable regenerative therapy.

Passive closure (without tension) of both ends of the wound ensures it heals with less reepithelialization, wound contraction, formation and remodeling of collagen fibers, and overall tissue remodeling is minimized (10–12).

The significance of primary wound closure is highlighted by examining the impact of membrane exposure on bone volume increases. In 2001, Machtei published a meta-analysis in which he examined the effects of barrier membrane exposure in GTR and in GBR. The author concluded that this postoperative complication has a negative effect on bone regeneration (13). Other published studies with similar results are available (14–16).

Early compared to late membrane exposure or removal has been the subject of other investigations. It appears that bone regeneration is predictable if a membrane can stay covered for a considerable amount of time, up to 6–8 months (17,18). Dense polytetrafluoroethylene membranes have demonstrated excellent properties. They are impenetrable to bacteria and can be left exposed, which is a great advancement in the field of guided bone regeneration (19,20).

Foreign objects, necrotic tissue, a weakened blood supply, and wound tension are all factors that hinder wound healing in a healthy person. These elements could help to explain why there is less bone development surrounding exposed membranes. An open wound contaminating the membrane with oral microbiota is another potential explanation for the decreased amount of bone production (21,22).

Achieving and sustaining primary closure requires proper flap design, tension-free flap approximation, and wound site care following surgery. Flaps should be properly planned and implemented to provide passive closure without putting tension on the edges of the incision (8).

Good Angiogenesis with Satisfactory Blood Supply

Good angiogenesis provides the necessary blood supply and transport of undifferentiated mesenchymal cells to the defect (8,9).

A blood clot forms in the defect area 24 hours after the surgical procedure (GTR or GBR). It is subsequently resorbed by neutrophils and macrophages and replaced by young granulation tissue. Granulation tissue is extremely rich in blood vessels. It is these blood vessels that are fundamental to the formation of osteoid and its subsequent mineralization (8,23). This mineralized bone tissue will subsequently remodel and form mature lamellar bone (24). The close correlation between newly formed blood vessels and the formation of osteoid in the immediate vicinity has long been demonstrated (25). It has been demonstrated that it takes six to nine months for the wound space to fully fill, first with a blood clot and subsequently with new bone (26).

The vascular supply for nourishing the new tissue in the barrier membrane, which safeguards flaws, primarily derives from blood vessels originating in the marrow (8).

Buser et al. discovered that the implementation of cortical perforations (i.e., intra-bone marrow penetration) facilitated the migration of cells possessing angiogenic and osteogenic capabilities (27). There are other studies that find that perforating the cortical bone positively affects the amount of newly formed bone. It has been proposed that the cortical plate may serve as a temporary barrier to the infiltration of beneficial cells and tissue elements from the marrow, as the resorption of cortical bone must occur prior to the accessibility of bone-forming components (28,29).

Barrier Function for the Required Period of Time

The guiding biological principle of GTR and GBR lies in the use of a physical barrier to inhibit the proliferation of gingival epithelial and connective tissue and thus allow slower regenerating tissues to repair the defect (30,31).

For resorbable membranes, it is of utmost importance that they resorb once they have been able to fulfil their barrier function. A degradation profile that works with the tissue regeneration process, which takes four to six weeks, is crucial. After serving its purpose, the membrane should ideally completely dissolve and leave no unwanted materials (8,32).

Securing and Maintaining the Defect Area

Securing and maintaining the defect area is necessary to allow proliferation of the slower regenerating tissues when the faster regenerating tissues are blocked (9,33).

By avoiding membrane collapse brought on by the pressure of surrounding tissues, reinforced membranes enable space maintenance. The addition of titanium mesh to the membrane increases its strength and permits it to be adjusted to the contour of the osseous defect (8).

The literature that is now available suggests that the use of reinforced membranes or extra bone grafts is more advantageous when a sizable volume of bone is needed for implant placement (8).

When more bone repair is needed, creating space using a barrier membrane is essential. As was already noted, absorbable membranes offer a number of advantageous characteristics. Membrane collapse, which could be brought on by the pressure of the soft tissue above, is a significant problem with utilizing an absorbable membrane alone. Numerous methods have been devised to surmount this obstacle. The use of coronally advanced flaps, bone grafting materials beneath the membrane, and other mechanical support techniques such as internal membrane frameworks, screws, or pins have all been tested and found to be effective (34,35).

Stable Blood Clot

A barrier membrane serves two purposes. Apart from keeping out undesirable cells, it also helps to keep the blood clot stable (8,9).

Initial clot attachment and wound stability are crucial for the healing process (36).

Cytokines (such as interleukin-1, interleukin-8, and tumor necrosis factor), growth factors (such as platelet-derived growth factor, insulin-like growth factor, and fibroblast growth factor), and signaling molecules that attract clearing cells to the wound site are abundant in the initial blood clot. Specifically, platelet-derived growth factor is a strong mitogen and chemoattractant for monocytes and neutrophils (37). The initial highly vascular granulation tissue is

derived from the blood clot. The first intramembranous bone growth and remodeling then takes place in the granulation tissue (38).

Regenerative therapy utilizes various biomaterials that have different mechanical properties, biological properties (biocompatibility, osteoconductivity, resorbability, etc.), and success rates. Assessing their tissue behavior requires clinical, radiological, histological, and histomorphometric examinations (39,40).

CONCLUSION

Both a high degree of technical proficiency and a comprehensive understanding of the fundamentals of wound healing are necessary for predictive regeneration.

The basic principles that are necessary to achieve predictable regenerative outcomes are primary wound closure, good angiogenesis, barrier function for the required period of time, securing and maintaining the bone defect area, and keeping the blood clot stable.

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