ESSENTIALS ON GUIDED BONE REGENERATION (GBR)

INTRODUCTION

Guided bone regeneration (GBR), is one of the advancing modalities for correcting bony defects and aims to achieve bone regeneration (Dahlin et al. 1988). GBR is a surgical procedure that involves the placement of barrier membranes with or without bone grafts and/or bone substitutes.1 Major function of barrier membrane includes: providing stability to the bone graft, preventing the overlying soft tissue from collapsing into the defect, preventing competing non-osteogenic cell from migrating into the site, and accumulating growth factors.

Although the concept was initially proposed for the regeneration of tissues associated with the periodontium of a tooth, the proof of principle was soon applied to regenerate edentulous alveolar ridges.

Osseous regeneration by GBR has been governed by the migration of pluripotent and osteogenic cells (e.g. osteoblasts derived from the periosteum and adjacent bone and bone marrow) to the bone defect site and exclusion of cells impeding bone formation (e.g. epithelial cells and fibroblasts).2

HISTORICAL BACKGROUND

Berg proposed in 1947 that bone grafts may raise the paraspinal muscles from decorticated laminae, allowing granulation tissue to grow in the empty area. This would increase the likelihood and speed of osteosynthesis in the spine. Shortly after, Hellstadius put Berg's idea to the test by raising muscles from the cortes of a rabbit's femur that had been roughened up using stainless steel cups and rings. He came to the conclusion that if the soft components were kept apart, bone would not grow in granulation tissue. In 1959, Hurley et al first described the principle of placing membrane between a bone defect and the surrounding soft tissues, (later termed as Guided bone regeneration).3

Barrier membranes were initially evaluated in the 1950s and 1960s for osseous face reconstruction by Nyman, et al. by Bassett, et al. and Boyne, et al.4

GTR was first developed in the early 1980s by Nyman et al.5

Murray first pronounced the procedure of placing barrier membranes for regeneration of lost bone in reduced alveolar width. Nyman and Gottlow introduced the term guided bone regeneration (GBR) in the 1980s as a result of GTRs. Occlusive barriers were used in periodontal healing studies to prevent the migration of cells from gingival connective tissue and epithelium to the periodontal defect, which can obstruct tissue regeneration.6

Early research on GBR was led by Dahlin and colleagues in an effort to address the challenging issue of reconstructing significant osseous abnormalities in the jaws and for the treatment of the atrophic maxilla or mandible.7

PRINCIPLES OF GUIDED BONE REGENERATION

**Basic Principle**

The intention of GTR is to save the connective tissue from getting in contact with the root surface by means of sandwiching a membrane between the flap and root. By selectively inducing cells from the periodontal membrane on the foundation floor, periodontal tissue is then renewed. Melcher created the idea of directed tissue regeneration for the first time in 1970.8

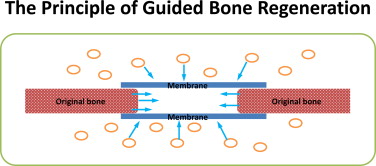


Image source: Rakhmatia et al. Principle of Guided Bone Regeneration. 2013. 57.10.1016/j.jpor.2012.12.001.

**Biological Principle**

Wang et al. in 2006 described 4 major biologic principles (i.e., PASS) necessary for predictable bone regeneration:

1. *Primary Closure*

True healing through primary aim is frequently challenging to accomplish. But primary wound closure, which establishes an environment that is unaffected/unaltered by external bacterial or mechanical damage, is a crucial surgical paradigm for GBR.

1. *Angiogenesis*

According to the GBR's guiding principles, the addition of bone grafting materials and membranes facilitates osteogenesis by potentially releasing bone morphogenetic proteins. A blood clot forms during the first 24 hours, is cleared by neutrophils and macrophages, and is followed by the beginning of granulation tissue production over the next days and weeks. De novo bone growth and newly generated blood vessels have a close link.9 Blood vessels, which are abundant in the granulation tissue, play a crucial role in the creation of osteoid and the subsequent mineralization of the tissue to form woven bone.10 The role of the blood clot in the repair of bone deformities was also emphasised by Melcher and Dryer.11

1. *Space Creation/Maintenance*

One of the guiding principles of GBR is to provide sufficient room for bone regeneration. To ensure the growth of bone-forming cells while keeping out undesirable epithelium and connective tissue cells, space is required. By avoiding membrane collapse brought on by pressure from tissues above, reinforced membranes help maintain space.

1. *Stability*

A barrier membrane serves two purposes: it keeps out undesirable cells and stabilises the blood clot.12 In order for a wound to heal, early clot attachment and wound stabilisation are crucial. Interleukin-1, Interleukin-8, and tumour necrosis factor are only a few of the cytokines, growth factors, and signalling molecules that are abundant in the early blood clot and help to draw healing cells to the wound site. Particularly for neutrophils and monocytes, platelet-derived growth factor is a powerful mitogen and chemoattractant.13

The barrier membrane placement should result in:

*Cell exclusion*: The barrier membrane is employed in GBR to prevent gingival fibroblasts and/or epithelial cells from entering the wound and producing fibrous connective tissue.

*Tenting*: A technique in which the membrane is carefully fitted and applied so that a space beneath the membrane is established, entirely isolating the defect to be regenerated from the overlaying soft tissue. It is critical that the membrane be cut so that it extends 2 to 3 mm beyond the defect edges in all directions. The membrane's corners should also be rounded to prevent accidental flap perforation.

*Scaffolding*: This tented space is first occupied by a fibrin clot, which acts as a scaffold for progenitor cell in-growth. The cells in GBR will come from neighbouring bone or bone marrow.

*Stabilization*: During healing, the membrane must also protect the clot from being disturbed by movement of the underlying flap. As a result, sutures, small bone screws, or bone tacks are frequently, but not always, used to secure it in place. At times, the edges of the membrane are merely tucked beneath the flap margins during closing, giving stability.

*Framework*: The membrane must be stabilized to prevent collapse where essential, such as in non-space maintaining defects such as dehiscence or fenestrations.14

INDICATION FOR GBR

1. Deficiencies in the local alveolar process (horizontal or vertical).

2. Bone filling of the immediate implant

3. Implant-related dehiscence and fenestration.

4. Bone abnormalities caused by implant failure.

5. Remaining bone lesions

6. Aid in the healing of perforations in the sinus membrane

GRAFT MATERIALS

GBR is a surgical procedure that uses barrier membranes with or without particulate bone grafts and/or bone substitutes.

Classification of barrier membranes:

Membranes used for periodontal regeneration are characterized primarily by their ability to resorb:

1. Expanded Non-Absorbable e-PTFE (Polytetrafluoroethylene) Gore-Tex d-PTFE (High Density Polytetrafluoroethylene) Titanium Reinforced PTFE Titanium Mesh

2. Polymeric (vicryl, atrisor, Epiguide) and resorbable materials derived from collagen.15 membranes for controlled bone regeneration:16

The first generation of barrier membranes developed in the 1960s and 1970s aimed to achieve an appropriate combination of physical properties that would match those of the replaced tissue with minimal toxic response in the host.

The second generation of barrier membranes were designed to be absorbable so that surgical removal was not necessary. There are two broad categories of bioresorbable membranes: natural and synthetic membranes.

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| --- | --- | --- | --- |
| Natural bone graft and substitute materials. | | | |
| Material Type | Forms Available | Material Source | Examples of clinically used bone grafts |
| Cortical  Allograft | Fresh, frozen,  freeze-dried  Whole bone  segments, block,  pieces | Mineralized  cortical allograft | MinerOss  CorticalTM |
| Cancellous  Allograft | Fresh, frozen,  freeze-dried  Chips, wedges, pegs,  powder | Mineralized  cancellous  allograft | MinerOss  CancellousTM |
| Demineralised  Bone Matrix | Putty, moldable  pastes, blocks,  particulates, powder | Human DBM | Dynagraft  D PuttyTM  OpteformTM  Grafton  DBMTM |
| Deproteinised  bovine bone | Block, granules,  particulates | Bovine | BioOssTM  OsteoGrafTM  CeraboneTM |
| Algae-based | Granules | Red algae | AlgiporeTM |
| Coral-based | Block, Granules | Marine coral | ProOsteonTM  BioCoralTM  InterPoreTM |
| Synthetic bone grafting materials. | | | |
| Material Type | Forms Available | Examples of clinically used bone grafts | |
| Hydroxyapatite | Blocks, wedges and  granules | OstimTM  EndobonTM | |
| Tricalcium  phosphate  ceramics | Blocks, cylinders,  wedges, granules | CerasorbTM  OSferionTM  OrthograftTM | |
| Biphasic calcium  phosphate  ceramics | Moldable putty,  granules | MASTERGRAFTTM | |
| Bioglasses | Particulates | PerioglasTM  BiogranTM | |
| Calcium  phosphate  cements | Injectable paste,  moldable putty | NorianTM  ChronOS  injectTM  HydrosetTM  BoneSourceTM | |
| Calcium sulfates | Various sizes pellets | OsteoSetTM | |
| Polymers | Particulates,  granules, ready to  use in syringe | Bioplant HTR  Synthetic BoneTM | |
| Metals | Mesh/membrane  available in lateral  and papilla design  forms | OSS BuilderTM | |
| Composites | Putty, granulate,  block, ready to use  “QD” | NanoBoneTM  (nanocrystalline  HA/silicon  dioxide) | |
|  | Paste | Fortoss VitalTM  (\_-TCP/calcium  sulphate) | |
|  | Blocks, microchips,  plate, granules,  wedge, cylinder, rod | SmartBoneTM  (DBM/polymer/collagen) | |

Table1: Table Source Zhao R. Bone Grafts and Substitutes in Dentistry. 2021. doi: 10.3390/molecules26103007.

SURGICAL PROCEDURE

Step 1: The flap is designed according to the following five principles.

A. The bone defect should be accessible

b. Maintenance of blood supply to the elevated valve and adjacent tissues

C. Preservation of the interdental papilla

d. Ensuring sufficient flap advance

E. Allows primary closure without tension

A midline, full-thickness incision is made between the teeth, preserving the interdental papilla. Two full-thickness vertical cuts are made to the bone on both sides, starting at the base of the vestibule and continuing coronally in one continuous cut to meet the ridge cut.

Step 2: Preparing the recipient site

The bony defect is cleared of granulation tissue and tissue plaques using curettes and reciprocating chisels. Cortical perforations (decortications) are then made with a #1 or #2 round bur using high speed with copious irrigation to create bleeding at the surgical site. Decortications are designed to increase blood flow and migration of osteogenic progenitor cells from the bone marrow to the augmentation site.17

Step 3: Release the cuts

Periosteal release incisions are made with a sharp 15 C blade on the inner apical part of the flap, creating a 2-3 mm thick dissection.

Step 4: Graft Materials and Membrane Placement

Step 5: Stabilization of the graft material and barrier membrane

Step 6: Suturing to advance the flap coronally

Step 7: Suturing to provide primary closure

Final tissue adaptation is achieved using multiple intermittent regularly spaced closure incisions.

COMPLICATIONS ASSOCIATED WITH GBR

Postoperative complications occurring after periodontal surgery can be categorized as following

A. Widespread complications arising after periodontal surgery:

* Bleeding
* Swelling
* Postoperative pain
* Root hypersensitivity
* Improved enamel mobility
* Not on-time wound healing
* Trismus
* Postoperative bacteremia
* Flavor adjustments
* Bruising

B. Complications springing up because of the surgical treatment hired.

* Local anaesthesia linked
* Flap associated
* Graft associated
* GTR membrane related
* Suture related
* Periodontal dressing associated18

Complications that are specifically related to GBR are mentioned below:

Complication classification associated with non-resorbable membrane.

Complications can be classified as either healing (Class I to IV) or surgical (A to C).

Healing complications:

Class I: Small membrane exposure (≤ 3 mm) without purulent exudate

Class II: Large membrane exposure (> 3 mm) without purulent exudate

Class III: Membrane exposure with purulent exudate

Class IV: Abscess formation without membrane exposure

Surgical complications:

• A: Flap damage

• B: Neurologic complications

• C: Vascular complications

CONCLUSION

It can be concluded that GBR can predictably lead to regeneration of critical maxillofacial defect sizes and new bone formation through a synchronized progression of events recapitulating intramembranous ossification. The available preclinical and clinical evidence suggests that GBR represents a successful therapeutic approach for the treatment of peri-implant bone defects and for preserving the dimensions and configuration of the alveolar cavity after tooth extraction. Preclinical and clinical studies investigating the physiology and pathophysiology of the healing process after GBR application at the molecular level are warranted in order to develop and implement new therapeutic strategies, e.g., tissue engineering, drug delivery, and/or gene therapy aimed at promoting bone formation and regenerative potential after GBR treatment .

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