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Guided tissue regeneration in peri-radicular surgery

Gabriele Baniulyte [a], Lorna Burns [b], Kamran Ali [c,*]

[a] Academic Clinical Fellow in Oral Surgery, University of Plymouth
[b] Lecturer in Evidence Based Healthcare – Information Specialist (Education), University of Plymouth
[c] Professor of Oral Surgery, Qatar University College of Dental Medicine, QU Health

A B S T R A C T

Guided tissue regeneration techniques have been available in dentistry for decades. Primarily used for periodontal surgery and implant placement, their usefulness in periapical surgery has been getting increased attention. From the currently available evidence, guided tissue regeneration can improve patient outcomes. As a result, this technique might become more common in the future. Therefore, this review outlines the main uses of guided tissue regeneration and provides a brief summary of evidence surrounding it, with particular focus on periapical surgery.

Clinical relevance

This article highlights the advances in guided tissue regeneration field and in particular its uses in periapical surgery.

Objectives

The reader should understand that guided tissue regeneration techniques can potentially improve the outcomes of periapical surgery.

Background

Guided tissue regeneration (GTR) is a surgical technique which has been gaining popularity in dentistry. Its aim is to regenerate dental supporting tissues to aid tooth and implant retention. Primarily used in periodontal surgery, it targets the reconstruction of periodontium by helping alveolar bone regeneration and collagen fibre insertion into the newly formed cementum [1]. GTR does this by stabilising the blood clot which allows wound healing by primary intention and protects the defect from gingival ingrowth [2]. Recently its use has been explored in periapical surgery procedures where repeat non-surgical endodontic treatment is not practical, unlikely to be successful or a biopsy is necessary [3].

The use of GTR in Dentistry was first deployed by Nyman et al., in 1982 [1]. Numerous experimental animal studies followed confirming clinical success of this technique and clinicians started employing it in periapical surgery. A questionnaire sent out to the members of the American Association of Endodontists in 2011 identified that 40% use GTR techniques when performing periapical surgery, especially in through-and-through lesions [4]. No similar study has been carried out in the UK.

Substantial evidence is available regarding the positive impact of GTR on patient outcomes in periodontology as well as implant dentistry. A meta-analysis carried out in 2017 found that periodontitis patients treated with GTR had improved healing outcomes which could be observed even after 10 years [5]. In implantology, GTR technique is frequently used when carrying out guided bone regeneration and has also proven to be beneficial in improving patient outcomes [6].

Rationale of GTR in periapical surgery

The ultimate goal of the use of GTR in periapical surgery is to regenerate periapical tissues, such as periodontal ligament, cementum and alveolar bone [7]. This goal is achieved by creating an optimum healing environment and excluding the proliferating cells which are undesirable due to their interference with tissue regeneration [7]. GTR employs three main principles – generation of stem cells, scaffolding and growth factors [8]. However, healing of the periapical lesion is complicated by the presence of a non-vital tooth which can contaminate the apical area and reduce its healing capacity. Therefore, all efforts must be made to ensure the bacterial load within the root canal and the periapical lesion itself has been reduced, leaving the wound as clean as possible.

One of the main factors influencing the success of GTR in periapical surgery is the lesion size. The best outcomes manifest in large combined periodontal-endodontic lesions or large through-and-through lesions, especially >10mm in diameter ([7,9]). Another factor to consider is the nature of the lesion. Naturally occurring lesions will already have connective tissue attachment present between mucosa and root surface and therefore a membrane is not necessary; whereas if the lesion is of pathologic origin, GTR is suggested to prevent junctional epithelium from migrating apically [9].

A well-performed endodontic treatment is the gold standard for teeth with periapical pathology and allows for the healing of the lesion [10]. However, in certain cases it is unlikely to improve the current situation or is simply impractical [3]. In these cases, in order to retain the tooth, the operator would have to consider a surgical approach which,

* Corresponding author.
E-mail address: ali.kamran@qu.edu.qa (K. Ali).

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when carried out well, has a success rate of over 90% [3]. The success is improved when the operator uses enhanced magnification, ensures minimal root resection bevel and prepares the 3-4mm root end using an ultrasonic instrument tip following which a new biocompatible root-end filling material is placed ([11,12]).

GTR periapical surgery technique

The aim for periapical wound healing after surgery is to regenerate lost alveolar bone, cementum as well as the periodontal ligament [13]. In order to ensure this happens, GTR techniques have been employed and have shown to be effective and successful [13–15].

Periapical surgery starts by obtaining adequate anaesthesia to ensure patient comfort. A strong consideration should be given to using good light and magnification as this has shown to improve the outcome of the surgery [8]. Following this, a surgical flap is reflected with minimal trauma. The design of the flap is based on clinical as well as radiographic findings. These include width of gingival tissues as well as gingival biotype, the location of the restoration margin, the location of the periapical lesion and the patient's aesthetic concerns.

Bone removal is done by creating a minimal osteotomy window, which exposes the periapical lesion and the apex of the root. At this point periradicular curettage is carried out and, if needed, a biopsy specimen taken for microbiological examination. The tip of the root (usually around 3mm) is resected with minimal bevel and haemorrhage achieved. In certain cases, application of methylene blue dye (1-2%) can assist with the inspection of the root surface in search for root fractures, accessory canals and poorly condensed root-end filling. Root-end cavity is prepared using ultrasonic or sonic microtips to a depth of 3mm, following the original path of the root canal. At this point a filling is placed in the root-end cavity, usually mineral trioxide aggregate (MTA). MTA has low solubility, great biocompatibility and adheres well to the cavity walls [16]. At this point GTR technique would be employed. An appropriate material and membrane is selected, cut to the size which is slightly larger than the defect so that the edges of the membrane lie on sound bone. The flap is then carefully replaced and sutured. A radiograph can be taken at this point or during the review appointment [17].

What GTR options are available for periapical surgery?

There are numerous GTR options currently in the market and therefore it might be difficult to choose which one to use. An important factor to consider is whether the membrane is absorbable or requires removal. Absorbable membranes have been shown to have better outcomes, and this might be due to the fact that another surgery would be necessary to remove the membrane if it did not absorb naturally [7].

From non-resorbable membranes group, methylcellulose acetate was initially used the most. Unfortunately, it had a tendency to tear and therefore was replaced by non-resorbable ePTFE membrane (GORE-TEX). Most of the early studies of GTR were carried out using non-resorbable membranes, but clinicians were not happy with the need for an additional surgery for membrane removal, opening up the market for the creation of bioresorbable materials [18].

A number of bioresorbable membranes were initially developed, including calcium sulphate, collagen membrane and polymers of polyglycoside (such as polyglycolic acid, polylactic acid and polygalactate). They are all biocompatible and prevent unwanted cells from migrating into the defect by retaining their physical shape for 6-8 weeks; following which the absorption process starts. Their main disadvantage is epithelial downgrowth and membrane degradation [18].

Calcium sulphate membrane provides good adaptation to the defect and absorbs in approximately 30 days without triggering body reaction or inflammatory response. It acts as a scaffold due to its special binding and filling properties, but is more frequently used as GBR rather than GTR [18].

Collagen membranes are predominantly prepared from bovine and porcine type 1 collagen, which has to be mentioned to patients during the consent process. As certain patient groups might not consent to the use of animal-based products [19]. The resorption of the membrane is later carried out by neutrophils and macrophages [18]. Collagen promotes fibroblast proliferation and acts as vascular and tissue scaffold, making it ideal for GTR.

The synthetic membranes made of polygalactate, polyglycolic acid and polylactic acid are available as alternatives to collagen membranes. However, they remain in the body for approximately 20 weeks and are degraded by hydrolysis, which causes inflammatory response. The response does not appear to be harmful, but it may affect the regeneration of the tissues [18].

The latest advancements in the GTR explore the use of blood-derived products (BDPs), such as platelet-rich-plasma (PRP), platelet-rich-fibrin (PRF), leucocyte and platelet-rich-fibrin, platelet-derived growth factor, bone morphogenic proteins, enamel matrix proteins and parathyroid hormone. Each of these products has different mechanisms of action to promote soft and hard dental tissue healing and involve simulation of the physiological healing and tissue repair process. BDPs are being used together with GTR graft materials to improve patient outcomes in oral surgical procedures.

The most common derived blood-derived GTR products are PRP, and PRF. Platelets in these products are capable of releasing platelet-derived growth factor, improving the osteogenic potential which in turn improves lesion healing [20]. Blood-derived GTR products can be easily obtained by taking a sample of patient's blood and centrifugation. The process is simple and is not associated with any major risks. Other GTR materials involve bone substitutes and membranes, which can be classed as a foreign body, and can therefore produce a rejection reaction; however, blood-derived GTR products do not carry this risk.

The concept of regenerative potential of platelets was first introduced in 1974 [21]. Initial studies suggested that the growth factor is released when platelets, trapped within the fibrin matrix, are activated. These growth factors stimulate bone repair process, thus aiding in lesion healing [22]. Initially, PRP was the material of choice because of its ability to release concentrated growth factors, including insulin-like growth factor 1, transforming growth factor-beta and platelet-derived growth factor. These growth factors enhance the natural ability of blood clot to promote bone regeneration and improve wound healing. [23] Preparation of PRP is relatively simple – blood is collected, centrifuged in two steps and platelet concentrate polymerisation is induced using bovine thrombin and calcium chloride. [24] A natural human blood clot primarily consists of approximately 94% red blood cells, 5% platelets and less than 1% white blood cells, whereas a PRP clot has 4% red blood cells, 95% platelets and around 1% white blood cells. [25] This change in composition allows for increased concentration of growth factors, improving healing. However, disadvantages of PRP preparation became evident, such as the requirement for bovine thrombin and anticoagulation in the first step prior to centrifuging the sample and biochemical blood processing. [26] This encouraged further research in the field of GTR involving BDPs to take place to address these issues.

PRF was created in 2001 in France to address the shortfalls of PRP. [27] The aim of PRF production is to create a fibrin clot with trapped leukocyte cytokines and platelets, which play a vital role in the therapeutic potential of PRF. During wound healing, cytokines are used up instantly to regulate cell migration and proliferation, thus encouraging tissue repair. [28]; whereas platelets regulate the fundamental healing processes, such as cell migration, proliferation and angiogenesis. [29] The preparation of PRF involves collection of venous blood in a vacutainer without anticoagulant. The vacutainer is then placed in a centrifugal machine at around 3,000 revolutions per minute for 10 minutes, allowing different layers to form – lowest layer contains red blood cells, middle layer contains the fibrin clot, and the upper layer contains the acellular plasma. [27] The middle layer is of interest, as it contains the PRF. The downside of this technique is the time between the blood

Table 1
Summary of the most recent RCTs.

Author and year	Type of study	Follow-up (months)	Type of GTR used	Sample size (patients)	Outcome assessment method	Results	Shortcomings
Dhamija et al, 2020	RCT	12	PRP	32	Clinical; 2-D and 3-D imaging	Success rate of 87.5% in PRP group; 50% in control group with 3D imaging	Envelopes used for randomisation; lesion sizes not standardised.
Parmar et al, 2019	RCT	12	Resorbable collagen membrane	32	Clinical; 2-D and 3-D imaging	GTR did not improve the outcome	Lack of histological confirmation of healing; limited statistical power.
Dhiman et al, 2015	RCT	12	PRP	30	Clinical and 2-D imaging	GTR group showed better improvement in probing depths (P=.04)	Majority of patients were male; small sample size.
Goyal et al, 2011	RCT	12	PRP and collagen membrane/sponge	25	Clinical and 2-D imaging	No significant difference between groups	No control group; 2D radiographic evaluation only; large number of dropouts.
Taschieri et al, 2008	RCT	12	Bio-Oss with Bio-Glide	31	Clinical and 2-D imaging	GTR group had significantly better outcome	2D radiographic evaluation only; radiopacity of Bio-Oss may have interfered with healing evaluation.

collection and the start of centrifuging because the blood with start coagulating almost instantly without anticoagulant, so speed is of essence. There are some advantages of PRF over PRP, including a simplified process, haemostatic potential, no additives to the blood preparation and slower polymerisation improving the healing potential [26]. Because of this, numerous trials and case reports have been published investigating the use of PRF in clinical situations, with promising outcomes [30–32]

Is there evidence that GTR improves periapical surgery outcomes?

Evidence-based practice is at the forefront of dentistry. It integrates the most up-to-date high level clinical evidence into clinical practice in order to improve patient outcomes and reduce errors in decision making [33]. Although there have been a number of case reviews and case series published in the literature investigating the effects of GTR on patient outcomes, these are not high-quality evidence.

There have only been a handful systematic reviews carried out on this topic ([13,34]). Tsesis et al., (2011) carried out the latest systematic review of five randomized clinical trials (RCTs) [34]. The review identified a trend of improved outcomes in the GTR group, but the findings were not statistically significant, although the healing of the lesion had a better outcome in the GTR group if it was large or through-and-through.

More RCTs have been published since the last systematic review was carried out (Table 1). Parmar et al., investigated the effect of collagen membrane on the through-and-through lesion healing using 2-dimensional and 3-dimensional imaging [35]. Thirty-two patients were included in this study with periapical radiolucencies and followed up for 12 months, but no significant difference was found between the outcomes of the two groups. The drawback of this study is the limited sample size and short follow up period, although it should be noted that larger lesions take longer to heal. Therefore, some of the lesions which were classified as 'failed to heal' could have continued to regenerate and would be reclassified over time.

A number of RCTs have focused on the effect of BDPs in conjunction with GTR on clinical outcomes following periapical surgery. Dhiman et al., investigated healing outcomes PRF and PRP in conjunction with GTR techniques in periapical surgery [36]. Thirty patients were followed up for 12 months. This study found that the success rate was higher in the GTR group with statistically significant pocket depth reduction ($P < 0.05$). This study had a small sample size and the healing was assessed by two-dimensional radiographs only. Goyal et al., concluded that when PRF is used together with collagen sponge or collagen membrane, it reduces the periodontal pocket depth and clinical attachment level; it also improves periapical healing ($p < 0.05$) [9]. Unfortunately, this study was underpowered, and the results had to be generalised due to varying drop-out rates between groups.

The most recent RCT published by Dhamija et al., in 2020 investigated the effect of PRP on healing of through-and-through periapical lesions using two and three-dimensional imaging [37]. The results of this study favoured PRP group (87% success rate) versus control group (50% success rate) when measured on 3D assessment. Interestingly, the results were similar for both groups on 2D evaluation (93% success rate). Unfortunately, only 32 patients were involved in this study and the results were not statistically significant. Furthermore, the randomisation in this study was carried out using opaque envelopes and unfortunately the study protocol did not include blinding.

As mentioned above, all studies had small sample sizes and patients and the follow-up was limited to 12 months only. Bone healing can take longer than a year, depending on the size of the defect. Therefore, some lesions which were categorised as 'non-healing' could later show signs of improvement and might be re-categorised, changing the results of the study.

Risks of surgery

A valid consent must be obtained first. Therefore, the operator should have an informed discussion with the patient which includes the explanation of risks and benefits of the procedure, and what happens if this procedure is not carried out. The main risks for periapical surgery include the standard surgical risks: pain, bleeding, bruising, swelling, infection, damage to adjacent teeth, gingival recession and loss of papillary height. In addition to those, site specific risks should be explained: damage to anatomical structures such as mental nerve, maxillary sinus and nasal cavity; loss of graft material, membrane exposure, and wound dehiscence. The patient should also be informed of what happens if the procedure is not successful and the tooth is lost including the options for its replacement. Ultimately, the patient should be aware of all the risks associated with the procedure and the potential outcomes; only then an informed decision can be made and valid consent obtained [38].

Post-operative monitoring

Clinical monitoring following periapical surgery needs to be done for 12 months [39]. If on a radiograph periapical lesion appears to be persisting, the tooth should be followed up for another 3 years. There are

a number of outcomes which indicate success: soft tissue healing, no loss of function; absence of pain or symptoms; no sinus tract; radiological evidence of success (i.e., healing of periodontal ligament space).

Conclusions

Guided tissue regeneration techniques in periapical surgery have been researched into and positive clinical outcomes highlighted. The latest systematic review carried out in 2011 identified the need for more prospective studies. Since then, a number of new RCTs have been published; some of which include newer materials, such as PRP. Therefore, a new updated systematic review would be beneficial to inform us of the updated evidence on different GTR techniques in periapical surgery.

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