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Guided tissue regeneration techniques involving blood-derived products in periradicular surgery: a systematic review and meta-analysis protocol

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Review title

Guided tissue regeneration techniques involving blood-derived products in periradicular surgery: a systematic review and meta-analysis protocol

Abstract

Objective: To evaluate the clinical outcomes of standard periradicular surgery versus periradicular surgery with the use of guided tissue regeneration techniques, which involve blood-derived products, in patients undergoing periradicular surgery.

Introduction: Guided tissue regeneration techniques have been available in dentistry for decades. Primarily used during periodontal surgery and implant placement, their usefulness in periapical surgery has been getting increased attention. From currently available evidence, guided tissue regeneration can improve clinical patient outcomes. No systematic reviews have been carried out to investigate guided tissue regeneration techniques involving blood-derived products in periradicular surgery.

Inclusion criteria: Randomized controlled trials, which investigate the outcomes of guided tissue regeneration techniques involving blood-derived products versus standard periradicular surgery technique, will be included for review. Studies will be excluded if they contain patients who have previously undergone periradicular surgery or the treatment was carried out on unrestorable teeth (i.e. due to periodontal disease or root fractures).

Methods: The databases MEDLINE, Embase and CENTRAL will be used to locate published reports of studies. Reference lists of relevant past systematic reviews will be used to identify further studies. Unpublished studies will be sought using international trials registries and the repositories. Two reviewers will carry out independent screening of records for inclusion and the selected studies will be critically appraised prior to data extraction and synthesis. Meta-analysis will be performed if appropriate.

Systematic review registration number: PROSPERO 2020 CRD42020222663

Keywords: Apicectomy; Dental; Guided Tissue Regeneration; Periapical Disease; Periapical Surgery.

27 **Abstract word count:** 224

28 **Total manuscript word count:** 2441

Introduction

Guided tissue regeneration (GTR) is an aid to surgical techniques, gaining popularity in dentistry. It helps alveolar bone regeneration and targets the reconstruction of periodontium and collagen fibres, aiming to regenerate dental supporting tissues and aid tooth retention.[1] Optimum healing environment is created by excluding proliferating cells, which interfere with the regeneration of dental tissues.[2] In ideal clean conditions, the main principles of GTR are generation of stem cells, growth factors and scaffolding.[3] However, the periapical lesion forms due to a non-vital tooth with a necrotic pulp, which makes the apical area contaminated, complicating the healing process. Therefore, the periapical area must be as clean as possible to remove bacterial load and allowing GTR principles to work.

Guided tissue regeneration principles have been used extensively in periodontal surgery, where it is thought to stabilise the blood clot, which in turn allows for better wound healing, whilst at the same time protecting the area from gingival ingrowth.[4] In recent years its advantageous properties have been explored in periradicular surgery, especially where repeat standard endodontic treatment would not be successful or practical.[5]

The positive impact of GTR in periodontology and implantology has been proven in numerous studies. In 2017 a meta-analysis looking into GTR techniques during periodontal treatment identified improved healing outcomes, which were still evident 10 years later.[6] In implantology, GTR is frequently used together with guided bone regeneration and these techniques together have also shown improvements in patient outcomes.[7]

When it comes to GTR in periapical surgery, the lesion size appears to significantly influence the outcome of the technique. Large lesions (>10mm in diameter), combined periodontal-endodontic lesions and large through-and-through lesions have shown the best clinical outcomes.[2, 8] The outcome is also affected by how well-performed the initial endodontic therapy was, as this will change the healing process by providing a cleaner environment for GTR to work in.[9] However, in certain cases, such as when a tooth has a well-fitting post-core crown, a repeat endodontic treatment is not practical.[5] In this case periradicular surgery should be considered, with a documented average success rate of over 90%.[5] The outcome is influenced and improved by enhanced magnification, minimal apical resection bevel, preparation of 3mm root apex with an ultrasonic instrument, followed by a biocompatible filling material to seal the root-end.[10, 11]

The most recent systematic review on GTR in periradicular surgery was published in 2011, which reviewed five randomized controlled trials (RCTs).[12] It identified improved clinical outcomes in the GTR group when compared to standard treatment and found enhanced healing in large and through-and-through lesions with the use of GTR. Unfortunately, the results were not statistically significant.

The most recent development in the field of GTR investigates the use of blood-derived products, such as platelet-rich-plasma (PRP), platelet-rich-fibrin (PRF), bone morphogenic proteins, platelet-derived growth factor, parathyroid hormone and enamel matrix proteins. All of these work in different mechanisms and are thought to stimulate healing of both soft and hard dental tissues by imitating tissue repair process and physiological lesion healing.[13] PRP and PRF seem to be investigated the most as a GTR involving blood-derived products option. They allow the formation of fibrin network whilst combining stem cells, leukocytes, platelets and cytokines together. Furthermore, the platelets in this mix are able to release platelet-derived growth factor, enhancing the osteogenic potential and therefore improving the healing of the lesion.[13] Blood-derived products are relatively easy to acquire, as they only need patients' blood sample, which is processed in a centrifugal equipment for the separation of blood products. Therefore, the associated risks with this procedure are minimal. Of note, the other GTR materials involving membranes and bone substitutes would have to consider the possibility of rejection (as they would be classed a foreign body), whereas blood-derived products do not carry this risk.

Dhiman et al investigated GTR involving blood-derived products versus standard periradicular surgery technique and found statistically significant reduction in pocket depth when GTR was used.[14] Goyal et al studied PRP in combination with collagen sponge or membrane, which again identified statistically significant periapical healing in favour of GTR.[8] The most recent study carried out by Dhamija et al looked at clinical and radiographic outcomes of PRP on large through-and-through lesions.[15] The results were in favour of PRP group versus control.

Since the last systematic review in 2011 was carried out investigating GTR in periradicular surgery, a number of new RCTs have been published investigating novel GTR techniques involving blood-derived products. Therefore, a systematic review is required to evaluate the current evidence available on clinical outcomes of the use of GTR techniques involving blood-derived products in periradicular surgery.

A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the JBI Database of Systematic Reviews and Implementation Reports was conducted and no current or underway systematic reviews on this topic were identified.

Review question

Does the use of guided tissue regeneration techniques involving blood-derived products during periradicular surgery improve clinical outcomes when compared to a standard periradicular surgery procedure alone?

Inclusion criteria

Participants

Studies investigating adults (over 18 years old) undergoing periradicular surgery for an endodontically treated tooth will be included. No restriction will be placed on the gender or ethnicity of patients, country of origin, patients' socio-economic status or health status. Studies, which involve patients who have previously undergone periradicular surgery, or where treatment was carried out on unrestorable teeth (i.e. due to periodontal disease or root fractures), will be excluded.

Interventions

The interventions to be reviewed are guided tissue regeneration techniques involving blood-derived products used to cover the defect in the bone, which remains following the removal of periradicular infection, at the end of periradicular surgery.

The procedure begins with adequate anaesthesia and raising of a surgical flap. Bone removal is done by creating a small osteotomy window, and exposing the apex of the root as well as the periradicular lesion. Curettage is carried out and the tip of the root resected. The root-end is then cleaned with an ultrasonic microtip and a filling is placed at the disinfected root-end. Guided tissue regeneration material involving blood-derived products (such as platelet-rich plasma derivatives) is then positioned over the remaining defect in the bone, following which the flap is repositioned and sutured.

Comparator

The comparator will be periradicular treatment without guided tissue regeneration technique at the end of the procedure. The procedure begins with adequate anaesthesia and raising of a surgical flap. Bone removal is carried out by creating a small osteotomy window, and exposing the apex of the root as well as the periradicular lesion. Curettage is carried out and the tip of the root resected. The root-end is cleaned with an ultrasonic microtip and a filling is placed at the disinfected root-end. The flap is then repositioned and sutured, leaving the remaining defect in the bone unfilled.

Outcomes

The review aims to investigate if the use of guided tissue regeneration techniques involving blood-derived products allows for a higher success rate of retaining a tooth free of clinical and radiological symptoms and signs of failure. The outcome will be measured using Molven's criteria, as outlined below.[16]

Failure to heal will be noted where clinical sign or symptom was present indicating failure (such as pain, sinus tract, tenderness to percussion or palpation, swelling, loss of tooth). Radiographically failure to heal would be noted if there was no reduction in the lesion size or if there was an enlargement of the lesion size following treatment. Success will be noted, if the treated tooth is free of clinical and radiological symptoms and signs of failure, as outlined above.

The trials will be examined for four possible outcomes: complete healing, incomplete healing, uncertain healing, and failure to heal. These outcomes will be based on clinical and radiographic evaluation. The outcomes will also be dichotomised to ''success'' or ''failure''. In this analysis, success will be noted for the following outcomes: complete and incomplete healing.

Types of studies

This review will include parallel and split mouth prospective randomized controlled trials only, involving humans. Split mouth trials should include the same participant receiving the intervention and the comparator, on separate teeth.

Methods

The proposed protocol for this systematic review will follow the Joanna Briggs Institute methodology for systematic reviews of effectiveness evidence.[17] It will also include the Preferred Reporting Items for Systematic Reviews and Meta-analysis checklist.[18] This review title has been registered with PROSPERO registry (CRD42020222663).

Search strategy

The search strategy created will aim to find both published and unpublished studies. An initial limited search on MEDLINE database was undertaken to identify published trials on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms as well as keywords used to describe the articles were used to develop a full search strategy. Appendix 1 includes the search strategy for all databases. Additionally, manual search will be carried out and the reference list of all included sources of evidence will be screened for additional studies. Studies published in English language will be included, with no publication date restrictions.

Information sources

The following databases will be searched to locate published reports of studies: MEDLINE, Embase, CENTRAL and Dentistry & Oral Sciences Source. Reference lists of relevant past systematic reviews will be used to identify further studies, adding the additional benefit of manual searching. Unpublished studies will be sought using international trials registries such as ClinicalTrials.gov and the repositories such as the BL EThOS database. Trials published in languages other than English will be excluded.

Study selection

Following the extensive search, all identified citations will be collated and uploaded into EndNote X7 (Clarivate Analytics, PA, USA) and duplicates removed. Following a pilot search test, titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. The duplicate articles will be removed. Potentially relevant studies will be retrieved in full and their citation details imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI) (JBI, Adelaide, Australia).[19] The full text of

selected trials will be critically appraised against the eligibility criteria by two independent reviewers. Reasons for exclusion of papers at full text stage, which do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion. The results of the search and the study inclusion process will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.[18]

Assessment of methodological quality

Eligible studies will be critically appraised by two reviewers independently. This will be done at the study level for methodological quality in the review using standardized critical appraisal instruments from the Joanna Briggs Institute for experimental studies.[19] Authors of papers will be contacted to request missing or additional data for clarification, where required. Any disagreements that arise will be resolved through discussion. All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possible). The results of critical appraisal will be reported in narrative form and in a table in a systematic review.

Data extraction

Data from the studies included in the review will be extracted. This will be done using the standardized data extraction tool to ensure all relevant data is captured.[19] The data extracted will include specific details about the population, study size, study methods, interventions, follow-up period, and outcomes of significance to the review objective, including type of guided tissue regeneration used and if a graft was used, comparator used as well as clinical and radiographic outcomes. Additional information, considered to be relevant, will also be recorded. Authors of papers will be contacted to request missing or additional data, where required.

Data synthesis

Studies will, where possible and appropriate, be pooled in statistical meta-analysis using JBI SUMARI.[19] Effect sizes will be expressed as either odds ratios (for dichotomous data) and weighted (or standardized) final post-intervention mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Statistical heterogeneity will be assessed using

the standard chi-squared or I squared tests. Statistical analyses will be performed using random effects or fixed effect model, depending on the quality and the amount of trials located.[20]

Sensitivity analyses will be conducted if appropriate. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation. A funnel plot will be generated using RevMan Software (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test) will be performed where appropriate to identify publication bias.

Assessing certainty in the findings

The evidence quality will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed.[21] A Summary of Findings (SoF) will be created using GRADEPro GDT 2020 (McMaster University, ON, Canada). The SoF will present the following information where appropriate: absolute risks for the treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision and risk of publication bias of the review results, where appropriate. The outcomes reported in the SoF will be: complete healing, incomplete healing, uncertain healing, failure to heal; overall success or failure.

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Conflicts of interest

There is no conflict of interest in this project.

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Appendix I: Search strategy

Search conducted using the limits outlined in the tables below for each database, carried out on 7th May 2021.

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to May 06, 2021>

1	Apicoectomy/	1563
2	Endodontics/	2344
3	Apicectomy.tw.	197
4	Apicoectomy.tw.	488
5	(periradicular adj3 surg*).tw.	159
6	(periapical adj3 surg*).tw.	409
7	(periapical adj3 resection).tw.	6
8	(endodontic adj3 surg*).tw.	958
9	(apical adj3 surg*).tw.	560
10	(apical adj3 resection).tw.	295
11	(root-end adj3 surg*).tw.	93
12	(root-end adj3 resection*).tw.	179
13	or/1-12	5743
14	Guided Tissue Regeneration/	2697
15	Guided Tissue Regeneration.tw.	1729
16	GTR.tw.	2209
17	(blood adj3 derived).tw.	11510
18	Platelet Rich Plasma/	4399
19	platelet rich plasma.tw.	10708
20	Platelet-Rich Fibrin/	507
21	platelet rich fibrin.tw.	1444
22	PRP.tw.	16260
23	PRF.tw.	3885
24	or/14-23	42543
25	13 and 24	112

Ovid Embase <1974 to 2021 May 06>

1	Apicoectomy/	199
2	endodontic surgery/	144
3	Apicectomy.tw.	194
4	Apicoectomy.tw.	407

5	(periradicular adj3 surg*).tw.	151
6	(periapical adj3 surg*).tw.	374
7	(periapical adj3 resection).tw.	4
8	(endodontic adj3 surg*).tw.	901
9	(apical adj3 surg*).tw.	808
10	(apical adj3 resection).tw.	342
11	(root-end adj3 surg*).tw.	89
12	(root-end adj3 resection*).tw.	175
13	or/1-12	3091
14	Tissue Regeneration/	25652
15	Guided Tissue Regeneration.tw.	1697
16	GTR.tw.	3100
17	(blood adj3 derived).tw.	17018
18	thrombocyte rich plasma/	13621
19	platelet rich plasma.tw.	14695
20	Platelet-Rich Fibrin/	1069
21	platelet rich fibrin.tw.	1464
22	PRP.tw.	23065
23	PRF.tw.	5257
24	or/14-23	83005
25	13 and 24	129

279 **Dentistry and Oral Sciences Source via EBSCOhost**

S1	DE "APICOECTOMY"	279
S2	DE "ENDODONTICS"	11,192
S3	TI (Apicectomy OR Apicoectomy) OR AB (Apicectomy OR Apicoectomy)	280
S4	TI (periradicular N3 surg* OR periapical N3 surg*) OR AB (periradicular N3 surg* OR periapical N3 surg*)	417
S5	TI (periapical N3 resection OR endodontic N3 surg*) OR AB (periapical N3 resection OR endodontic N3 surg*)	923
S6	TI (apical N3 surg* OR apical N3 resection) OR AB (apical N3 surg* OR apical N3 resection)	309
S7	TI (root-end N3 surg* OR root-end N3 resection*) OR AB (root-end N3 surg* OR root-end N3 resection*)	206
S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	12,207
S9	DE "GUIDED tissue regeneration"	1,412
S10	TI Guided tissue regeneration OR AB Guided tissue regeneration	1,017
S11	TI GTR OR AB GTR	514
S12	TI blood N3 derived OR AB blood N3 derived	56
S13	DE "PLATELET-rich plasma"	492
S14	TI Platelet-rich plasma OR AB Platelet-rich plasma	828
S15	DE "PLATELET-rich fibrin"	580

S16	TI Platelet-rich fibrin OR AB Platelet-rich fibrin	843
S17	TI (PRP OR PRF) OR AB (PRP OR PRF)	1,312
S18	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17	3,696
S19	S8 AND S18	162

CENTRAL via the Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Apicoectomy] explode all trees	83
#2	MeSH descriptor: [Endodontics] explode all trees	1438
#3	Apicectomy	25
#4	Apicoectomy	104
#5	periradicular NEAR/3 surg*	30
#6	periapical NEAR/3 surg*	81
#7	periapical NEAR/3 resection	1
#8	endodontic NEAR/3 surg*	113
#9	apical NEAR/3 surg*	102
#10	apical NEAR/3 resection	21
#11	root-end NEAR/3 surg*	10
#12	root-end NEAR/3 resection*	22
#13	{OR #1-#12}	1677
#14	MeSH descriptor: [Guided Tissue Regeneration] explode all trees	525
#15	Guided tissue regeneration	842
#16	GTR	413
#17	blood NEAR/3 derived	581
#18	MeSH descriptor: [Platelet-Rich Plasma] explode all trees	536
#19	Platelet-rich plasma	2230
#20	MeSH descriptor: [Platelet-Rich Fibrin] explode all trees	104
#21	Platelet-rich fibrin	769
#22	PRP	2570
#23	PRF	919
#24	{OR #14-#23}	5710
#25	#13 AND #24 in Trials	45
#26	#25 not (embase or pubmed):an	19