Effect of Guided Tissue Regeneration on the Outcome of Surgical Endodontic Treatment: A Systematic Review and Meta-analysis

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Abstract

Introduction: The use of guided tissue regeneration (GTR) techniques has been proposed as an adjunct to endodontic surgery in order to promote bone healing. Studies assessing the added benefits of GTR for the outcome of endodontic surgery are significantly variable in their treatment protocols, follow-up periods, and inclusion criteria, thus generating inconsistent and confusing results. The aim of this study was to evaluate the influence of GTR on the outcome of surgical endodontic treatment by means of a systematic review of the literature and meta-analysis. **Methods:** An exhaustive literature search combined with strict inclusion and exclusion criteria was undertaken to identify clinical studies that assessed the added benefit of GTR in endodontic surgery. **Results:** A trend of better outcome was found when GTR was used compared to control cases, but the results were not statistically significant. Lesion size, lesion type, and membrane type were identified as factors significantly affecting the outcome of GTR versus control cases. GTR techniques favorably affected the outcome of surgical endodontic treatments in cases of large periapical lesions and through-and-through lesions. A favorable outcome was found when using a resorbable membrane over using a nonresorbable membrane or graft alone. **Conclusions:** GTR techniques may improve the outcome of bone regeneration after surgical endodontic treatments of teeth with certain lesions. Additional large-scale prospective clinical studies are needed to further evaluate possible benefits of GTR techniques in endodontic surgery. *(J Endod 2011;37:1039–1045)*

Key Words

Endodontic surgery, guided tissue regeneration, meta-analysis, outcome

Surgical endodontic treatment is an option for teeth with apical periodontitis and may be indicated for teeth with periapical pathology when nonsurgical retreatment is impractical or unlikely to improve the previous results or when a biopsy is needed (1, 2). Modern endodontic surgical technique uses enhanced magnification, minimal root resection bevel, ultrasonic root-end preparation to a depth of 3 to 4 mm, and newer biocompatible root-end filling materials (3). A success rate of over 90% has been reported with this technique (2–4).

The final histologic results of the wound healing in endodontic surgery may be repair or regeneration depending on the nature of the wound; the availability of progenitor/stem cells; growth/differentiation factors; and microenvironmental cues such as adhesion molecules, extracellular matrix, and associated noncollagenous protein molecules (5, 6).

Complete periapical wound healing after periapical surgery includes regeneration of alveolar bone, periodontal ligament, and cementum (5). The use of guided tissue regeneration (GTR) techniques has been proposed as an adjunct to endodontic surgery in order to promote bone healing (7–10). Numerous studies on the clinical effectiveness of GTR techniques to promote healing and improve the outcome of surgical endodontic treatments have been published (5–9, 11–22). However, significant variability in their study designs, treatment protocols, follow-up periods, and inclusion and exclusion criteria generated inconsistent and confusing results (5–9, 11–22).

Evidence-based dentistry is an approach to oral health care that integrates the best available clinical evidence to support a practitioner's clinical expertise for each patient's treatment needs and preferences (23–25). Systematic reviews constitute the basis for practicing evidence-based dentistry (23, 25, 26). Thus, an evidence-based review of the available literature regarding the effect of GTR on the outcome of surgical endodontic treatment is of the utmost significance. The aim of the present study was to evaluate the influence of GTR on the outcome of surgical endodontic treatment by means of a systematic review of the literature and meta-analysis.

Materials and Methods

Criteria for Considering Studies for This Review

This systematic review included clinical studies that reported the use of guided tissue regeneration in surgical endodontic treatment in patients with apical periodontitis in endodontically treated teeth.

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The inclusion criteria included the following: (1) randomized clinical trials (RCTs), (2) a lesion location in the periapical area, (3) inclusion of GTR as a part of the surgical protocol (for the treatment group), (4) at least 1 year of follow-up, and (5) outcome evaluated according to Rud et al (27) and/or Molven et al (28). The exclusion criteria included the following: (1) previous endodontic surgery (resurgery cases), (2) teeth presenting with apicomarginal defects and teeth with periodontal disease (periodontal pockets and/or mobility), (3) root fractures and root perforations, and (4) a retrospective study design.

Search Methods for the Identification of Studies

The search covered all articles published in dental journals in English from 1966 to September 2010. The following electronic databases were searched: MEDLINE using PubMed search engine (http://www.ncbi.nlm.nih.gov/sites/pubmed) using the key words: apicectomy OR apicoectomy OR "periradicular surgery" OR "endodontic surgery" OR "apical surgery" OR "periapical surgery" OR "root-end surgery" OR "root-end resection" AND "regeneration," with the application of the following Entrez PubMed limits: "humans" and "English."

MESH received the following: ("apicoectomy"[MeSH Terms] OR "apicoectomy" [All Fields] OR "apicectomy" [All Fields]) OR ("apicoectomy" [MeSH Terms] OR "apicoectomy" [All Fields]) OR "periradicular surgery" [All Fields] OR "endodontic surgery" [All Fields] OR "apical surgery" [All Fields] OR "periapical surgery" [All Fields] OR "root-end surgery" [All Fields] OR "root-end resection" [All Fields] AND ("regeneration" [MeSH Terms] OR "regeneration" [All Fields]) AND ("humans" [MeSH Terms] AND English[lang]). The Scopus search (www.scopus.com) was performed using the following key words: apicectomy OR apicoectomy OR "periradicular surgery" OR "endodontic surgery" OR "apical surgery" OR "periapical surgery" OR "root-end surgery" OR "root-end resection" AND regeneration, with the following filters: articles, limited to dentistry, English language. The query received was as follows: TITLE-ABS-KEY(apicectomy OR apicoectomy OR "periradicular surgery" OR "endodontic surgery" OR "apical surgery" OR "periapical surgery" OR "root-end surgery" OR "root-end resection" AND regeneration) AND (LIMIT-TO[DOCTYPE, "ar"]) AND (LIMIT-TO[SUBJAREA, "DENT"] OR LIMIT-TO [SUBJAREA, "MULT"]) AND (LIMIT-TO[LANGUAGE, "English"]).

The search through the Embase database (http://www.embase.com) was performed by using the following key words: "apicectomy" OR "apicoectomy" OR "periradicular surgery" OR "endodontic surgery" OR "apical surgery" OR "periapical surgery" OR "root-end surgery" OR "root-end resection" AND "regeneration" and by applying Embase limits to "humans,'' "English," "article" and "Embase ONLY."

The MESH received the following: ('apicectomy' OR 'apicoectomy'/exp OR 'periradicular surgery' OR 'endodontic surgery'/exp OR 'apical surgery' OR 'periapical surgery' OR 'root-end surgery' OR 'root-end resection) AND 'regeneration'/exp AND [article]/lim AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim. Related articles and literature reviews that appeared in the MEDLINE search engine and their reference lists were manually checked.

Data Collection and Analysis

Selection of Studies

The articles were initially evaluated for relevance based on their titles and abstracts by three observers independently (IT, AT, and ER). Possibly relevant studies were subject to a full text evaluation. The full texts of the studies were obtained and reviewed for suitability based on the inclusion and exclusion criteria of this meta-analysis. Cases of disagreement were discussed together until agreement was reached. Eventually, the identified suitable articles were subject to data extraction, assessment of the methodological quality, and data synthesis and analysis.

Data Extraction

Data were extracted by three observers independently. Cases of disagreement were subject to joint evaluation by the observers until an agreement was reached. The parameters recorded for each study included authors' names, date of publication, and the following methodological parameters: study purpose; sample size; demographic details of the subjects, inclusion criteria; study design; randomization method, evaluators' blinding; homogeneity of the subjects.

Additional variables recorded for each study were lesion size (small if diameter <10 mm or large if diameter ≥ 10 mm), lesion type (through-and-through or four-wall lesion), type of membrane (resorbable or non resorbable), and whether the site was grafted or not.

Methodological Quality Assessment

The methodologic quality of the selected studies was evaluated independently and in duplicate by two reviewers (IT and MDF) as part of the data-extraction process. The trials were assessed on three main quality criteria: (1) sample size calculation, (2) concealed allocation of treatment, and (3) completeness of information on reasons for withdrawal from the study in each trial group. Further assessment was undertaken for secondary quality criteria, including the randomization method, the inclusion/exclusion criteria, the comparability of control and treatment groups at entry to the study, and the calibration and blinding of the evaluator(s) of outcome assessment. All the quality criteria (main and secondary) were assessed as either adequate or inadequate. The authors of the identified RCTs were contacted in request for clarifications or for providing missing information as needed.

In order to summarize the validity of studies, they were grouped into the following categories: (1) low risk of bias if all three main quality criteria were met (found adequate); (2) moderate risk of bias if one of the main criteria was not met or if two main criteria were not met but at least three of the secondary criteria were met, and (3) high risk of bias if none of the main criteria were met or if one main criterion and less than three secondary criteria were met. In case of discrepancy between the two reviewers, an agreement was reached by discussion. Otherwise, a third reviewer was consulted (ST) until consensus was achieved.

Data Synthesis and Analysis

All cases were graded according to the following four-item outcome classification: complete healing, incomplete healing (scar), uncertain healing, and failure. Outcome was assessed based on radiographic evaluation criteria (27, 28) and on clinical evaluation. A case was considered as failure, regardless of the radiographic evaluation, when a clinical sign or symptom was present, such as pain, swelling, tenderness to percussion or palpation, or sinus tract. In addition to the four-item outcome analysis, the outcome data were also dichotomized to a success/failure classification. For this analysis, the outcomes complete, incomplete, and uncertain healing were pooled together and considered as "success."

The statistical analysis was conducted using both the tooth and the patient as the analysis unit. Meta-analysis of the included studies was performed using the Mantel-Haenszel method for the dichotomized data, with a fixed-effect analysis model based on the odds ratio (OR). Results of the included studies were combined to estimate the pooled success rate and the 95% confidence interval (CI) using RevMan 5.0 (Review Manager, Copenhagen: The Nordic Cochrane Centre, The

TABLE 1. Studies Excluded from the Meta-analysis and Exclusion Criteria

Study	Exclusion criterion
Pompa et al, 1997 (30)	Case report
Dietrich et al, 2003 (14)	Treated apicomarginal defects
Marin-Botero et al, 2006 (16)	Treated apicomarginal defects
Sikri et al, 1986 (20)	Less than a 1-year follow-up
Pantchev et al, 2009 (29)	Retrospective study
Garrett et al, 2002 (15)	Outcome not evaluated according to Rud 1972 and/or Molven 1987 (27, 28)
Taschieri et al, 2007 (31)	GTR was not included as part of the surgical protocol

GTR, guided tissue regeneration.

Cochrane Collaboration, 2008). Forest plots were produced to graphically represent the difference in outcomes of treatment groups for all included studies using both the patient and the tooth as the analysis unit. The Fisher exact test was used to statistically assess the effect of the variables considered (ie, lesion size, lesion type, and type of membrane) on treatment outcomes for each treatment group. A probability of $P = .05$ was used as the level of significance.

Results

The search in MEDLINE database using the PubMed search engine resulted in 168 articles, of which 11 (6, 9, 10, 14–16, 18, 20, 21, 29, 30) were eligible for inclusion on the basis of their titles and abstracts and were subject to full-text evaluation. The other 157 articles were rejected based on the following: 23 were review articles, 24 were case reports, 4 were animal studies, and 106 articles were not relevant to the topic of the current study. The search with Scopus database resulted in 11 articles, all of which were previously identified by MEDLINE search.

The search with the Embase database resulted in 23 articles, of which one study (31) was eligible for inclusion on the basis of its title and abstract and was subject to full-text evaluation. The other 22 articles were rejected based on the following: 2 were review articles, 4 were case reports, 1 was an *in vitro* study, 11 were not relevant to the topic of the current study, and 4 were previously identified by Pubmed search. The manual search in the related articles and the reference lists of literature reviews yielded no additional relevant articles.

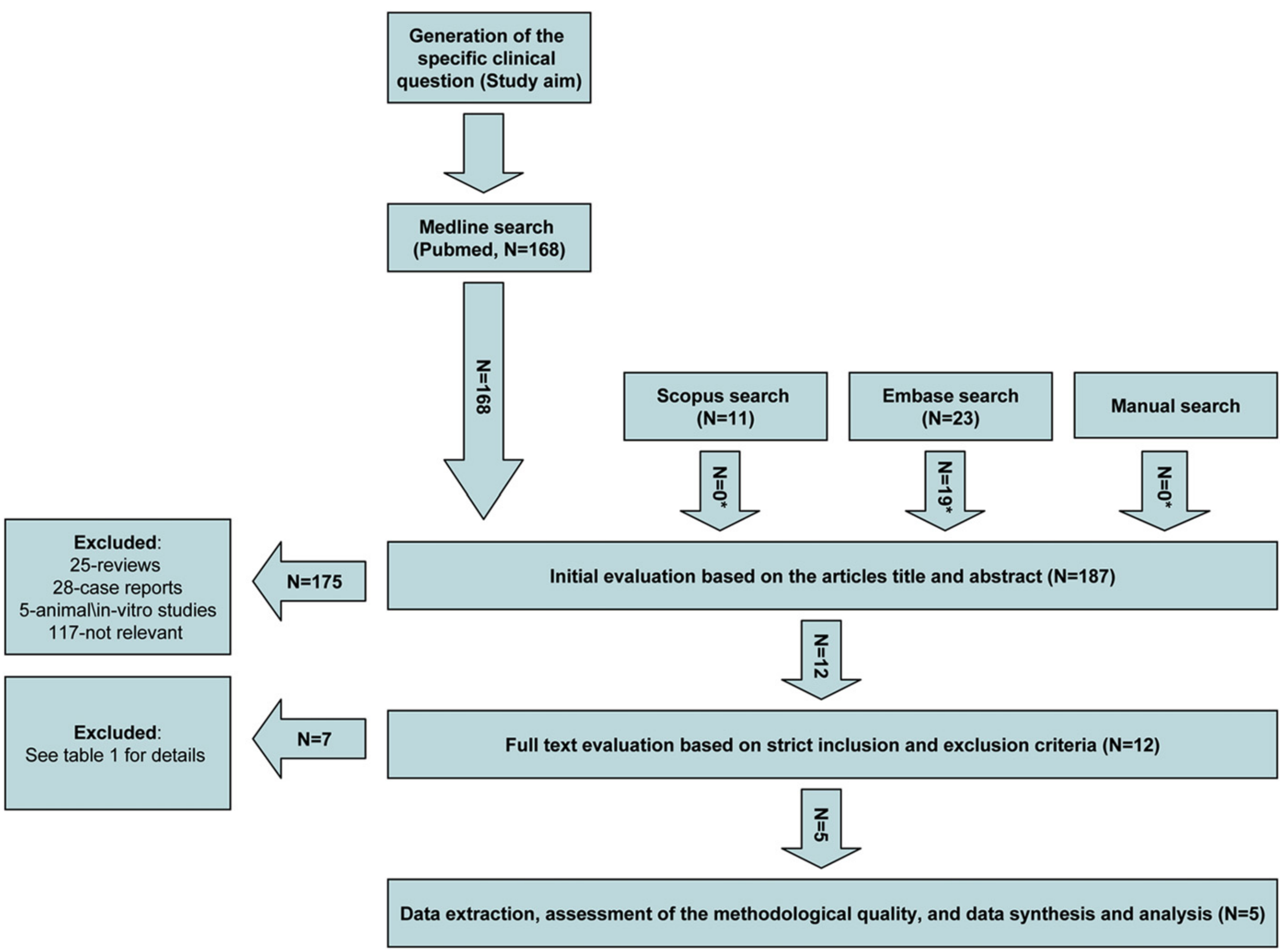

Figure 1. A flow chart of the systematic review process.

TABLE 2. Studies Included in the Meta-analysis and Treatment Outcomes Therein

Study	Study design	GTR group: Total number of teeth	GTR group: Complete healing, n (%)	GTR group: Incomplete healing, n (%)	GTR group: Uncertain healing, n (%)	GTR group: Failure, n (%)	Control group: Total number of teeth	Control group: Complete healing, n (%)	Control group: Incomplete healing, n (%)	Control group: Uncertain healing, n (%)	Control group: Failure, n (%)
Pecora, 1995 (18)	RCT	10	9 (90)	1 (10)	0 (0)	0 (0)	10	9 (90)	1 (10)	0 (0)	0 (0)
Pecora, 2001 (6)	RCT	10	7 (70)	2 (20)	0 (0)	1 (10)	10	3 (30)	5 (50)	0 (0)	2 (20)
Tobon, 2002 (10)	RCT	17	14 (82)	1 (6)	2 (12)	0 (0)	9	4 (44)	4 (44)	0 (0)	1 (11)
Taschieri et al, 2007 (21)	RCT	24	20 (83)	0 (0)	3 (13)	1 (4)	35	26 (74%)	0 (0)	7 (20)	2 (6)
Taschieri et al, 2008 (9)	RCT	17	15 (88)	0 (0)	1 (6)	1 (6)	14	8 (57%)	0 (0)	5 (36)	1 (7)

GTR, guided tissue regeneration; RCT, randomized controlled trial.

The 12 identified articles were subject to full-text evaluation. Following the full-text evaluation, seven articles were excluded (14–16, 20, 29–31). Table 1 shows the seven excluded studies and the reasons for exclusion.

Eventually, five articles (6, 9, 10, 18, 21) were included in the meta-analysis and were subject to data extraction, methodologic quality assessment, and data synthesis and analysis. Figure 1 presents a flow chart of the systematic review process. Table 2 shows the main features and the outcomes of the five studies included in the analysis. According to the methodologic quality assessment, one study (18) was judged to be at high risk of bias (category C), whereas the other four studies were considered at moderate risk of bias (category B).

From the meta-analysis of the five studies, a trend of a better outcome was found when GTR was used compared with control cases, but the results were not statistically significant, either in a tooth-based analysis (OR = 0.49; 95% CI, 0.13–1.88; $P = .30$, Fig. 2) or in a patient-based analysis (OR = 0.48; 95% CI, 0.12–1.86; $P = .29$, Fig. 3). In fact, although the weighted mean values were in favor of the GTR cases, the 95% CIs, graphically represented by the black diamonds, overlapped with the equivalence line (OR value = 1) in both plots. No significant heterogeneity among studies could be detected, which justified the use of the fixed-effects model.

Table 3 presents the variables that were included in the meta-analysis. The following presents the included variables effect on the treatment outcomes for each treatment group (Fisher exact test statistical analysis). In the GTR cases, small lesions showed a trend of better healing than large lesions ($P = .06$). In the control group, small lesions healed better than large lesions ($P = .006$) although scarce data on smaller lesions were available in the included studies. For either small or large lesions, cases treated with GTR healed better than cases treated without GTR ($P = .005$ and $P = .001$, respectively). Analysis of the lesion type revealed that for through-and-through lesions, cases treated with GTR achieved better results than control cases ($P = .02$), whereas for four-wall cases the use of GTR had no significant advantage ($P = .27$). Analysis of the effect of membrane type showed that more favorable outcomes were related to the use of a resorbable membrane either over a nonresorbable membrane ($P = .02$), over a graft without a membrane ($P = .006$), or over control cases (no graft, no membrane) ($P < .001$). Results for a nonresorbable membrane and graft without a membrane were not significantly different ($P = .06$), and both gave significantly better results than the control cases ($P = .007$ and $P = .006$, respectively).

Discussion

GTR techniques have been suggested as an adjunct to endodontic surgery in order to promote bone healing (7–10, 21). Several biomaterials were used as an osteoconductive scaffold in periapical surgery (10–14, 17, 22, 32–34), none of which achieved worldwide consensus. The aim of the present study was to search and evaluate the available literature concerning the influence of GTR on the outcome of surgical endodontic treatment by means of a systematic review of the literature and meta-analysis.

The variability in the results of studies assessing the benefits of GTR for the outcome of surgical endodontic treatment might be related to the lack of standardization in assessment criteria (2, 4, 27, 28). Therefore, to overcome heterogeneity of information, strict inclusion and exclusion criteria were applied to the identified studies.

Furthermore, only studies in which the treated cases were followed up for at least 1 year were included. Rud et al (35) reported a strong correlation between the outcome 1 year postoperatively and

Study or Subgroup	GTR Events	GTR Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Pecora 1995	0	10	0	10		Not estimable	1995
Pecora 2001	1	10	2	10	28.7%	0.44 [0.03, 5.88]	2001
Tobon 2002	0	17	1	9	29.9%	0.16 [0.01, 4.41]	2002
Taschieri et al. 2007	1	24	2	35	24.9%	0.72 [0.06, 8.39]	2007
Taschieri et al. 2008	1	17	1	14	16.5%	0.81 [0.05, 14.28]	2008
Total (95% CI)		**78**		**78**	**100.0%**	**0.49 [0.13, 1.88]**	
Total events	3		6				

Heterogeneity: Chi² = 0.65, df = 3 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)

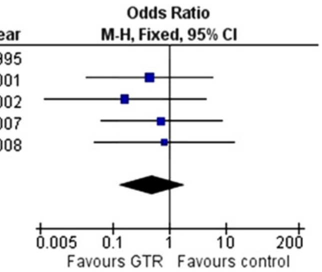

Figure 2. A forest plot of comparison: GTR versus control, tooth-based analysis. "Events" stands for failures. No heterogeneity among studies outcomes was found.

the outcome achieved at a longer (4-year) time period and recommended that a standard 1-year follow-up should be performed after the endodontic surgical treatment. Rubinstein and Kim (36, 37) evaluated cases considered healed 1 year postoperatively for an additional 5 to 7 years. The authors (36) found that 91.5% of the teeth that were assessed as healed after 1 year of observation remained healed at the end of the longer follow-up. Therefore, the pooled data presented in this meta-analysis may represent a good approximation of longer-term results.

In the present study, only studies in which the evaluated lesions were located at the periapical area were included. The important difference between endodontic and periodontal therapy is that the periodontium is usually healthy in endodontic treatment situations, and flap elevation is performed only for access, whereas periodontal treatment is initiated in diseased tissues. Furthermore, the periodontal defect is mostly an open wound, whereas the endodontic lesion is primarily a closed wound (5, 38). Complete periapical tissue regeneration has been previously shown even in the absence of membrane barriers and/or bone grafts in periapical surgery (2–4, 39–43) as opposed to potential severe periodontal tissue destruction caused by marginal periodontitis after open flap debridement without using membrane barriers and/or bone grafts.

In order to assess the overall effect of using GTR techniques on the outcome of endodontic surgery, a meta-analysis of the five included studies based on dichotomized data was performed. A trend of a better outcome when GTR was used as compared with control cases was found, but the results were not statistically significant. The fact that the meta-analysis did not provide significance may represent the "true" clinical value of GTR or may be a result of the insufficient total sample size in the analysis. Additional large-scale RCT studies assessing the added benefit of GTR techniques in endodontic surgery are required in order to shed light on this subject. In the present study, a number of variables were extracted from the studies, and their effects on the proportion of success and failure in GTR versus control groups were evaluated based on a four-item outcome classification.

Lesion Size

In small periapical lesions, resident osteoblasts, periodontal ligament cells, and cementoblasts might be capable of restoring damaged periapical tissues. However, in large periapical lesions, periapical wound healing requires recruitment and differentiation of progenitor cells/stem cells into osteoblasts, cementoblasts, and periodontal ligament cells (44). Andreason and Rud (45) proposed that if the size of the osseous defect is too large, osseous regeneration of the wound will not occur and the defect will heal by fibrous connective tissue repair. The present study confirms that GTR may be beneficial for the treatment of large periapical lesion.

Lesion Type

The results of the present study suggest that GTR may be beneficial for through-and-through lesions, whereas there was no significant advantage for the use of GTR for four-wall defects. A possible explanation may be related to the colonization of the healing wound by periodontal progenitor cells, a prerequisite for the formation of new cementum, a new periodontal ligament apparatus, and new alveolar bone (6, 9, 18, 21, 46). A key factor for this process is the periosteum because it may act both as a source of osteocompetent cells and as a barrier against the infiltration of epithelial cells into the healing site (6, 9). The use of a barrier for the treatment of large defects or "through-and-through" lesions may be advised because it is aimed to improve the self-regenerative process by blocking undesired proliferation of gingival connective tissue or migration of oral epithelium into the defect (6, 9).

The results of the present study revealed that favorable outcomes were related to the use of resorbable membrane, over the use of non-resorbable membrane, a graft without membrane, or versus the control cases. An ideal barrier material has to meet the following essential design criteria: it should be biocompatible (47), act as a barrier to exclude undesirable cell types from entering the secluded space adjacent to the root surface (5, 9, 47), allow the passage of nutrients and

Study or Subgroup	GTR Events	GTR Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Pecora 1995	0	10	0	10		Not estimable	1995
Pecora 2001	1	10	2	10	28.9%	0.44 [0.03, 5.88]	2001
Tobon 2002	0	16	1	9	29.4%	0.17 [0.01, 4.68]	2002
Taschieri et al. 2007	1	17	2	24	25.0%	0.69 [0.06, 8.25]	2007
Taschieri et al. 2008	1	14	1	11	16.7%	0.77 [0.04, 13.87]	2008
Total (95% CI)		**67**		**64**	**100.0%**	**0.48 [0.12, 1.86]**	
Total events	3		6				

Heterogeneity: Chi² = 0.56, df = 3 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.06 (P = 0.29)

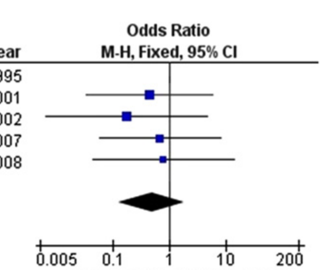

Figure 3. A forest plot of comparison: GTR versus control, patient-based analysis. "Events" stands for failures. No heterogeneity among studies outcomes was found.

TABLE 3. Summary of Evaluated Variables in the Meta-analysis

Study	GTR group: n (%)							Control group: n (%)			
	Lesion size		Lesion type		GTR procedure*			Lesion size		Lesion type	
	Small (<10 mm)	Large (≥10 mm)	Through-and-through	Four walls	Resorbable membrane	Nonresorbable membrane	Graft only w/o membrane	Small (<10 mm)	Large (≥10 mm)	Through-and-through	Four walls
Pecora, 1995 (18)	0	10 (100)	10 (100)	0	0	10 (100)	0	0	10 (100)	10 (100)	0
Pecora, 2001 (6)	0	10 (100)	10 (100)	0	0	0	10 (100)	0	10 (100)	10 (100)	0
Tobon, 2002 (10)	17 (100)	0	NA	NA	0	17 (100)	0	9 (100)	0	NA	NA
Taschieri et al, 2007 (21)	0	24 (100)	8 (33)	16 (67)	24 (100)	0	0	0	35 (100)	13 (37)	22 (63)
Taschieri et al, 2008 (9)	0	17 (100)	17 (100)	0	17 (100)	0	0	0	14	14 (100)	0

GTR, guided tissue regeneration; NA, not available.

*The graft material used: Pecora 1995, membrane only; Pecora 2001, medical grade calcium sulphate in various layers; Tobon 2002, synthetic bioactive resorbable graft of hydroxylapatite (OsteoGen; Impladent Ltd, Holliswood, NY); Taschieri 2007 and 2008, inorganic bovine bone mineral (Bio-Oss Spongiosa 0.5- to 1-mm particles; Geistlich Biomaterials, Wolhusen, Switzerland).

gases, allow tissue integration into the material without penetrating all the way through in order to prevent rapid epithelial down-growth on the outer surface of the material, provide stability to the overlying flap (47), capable of creating and maintaining a space adjacent to the root surface (9, 47), and comes in configurations that are easy to trim and to place (5, 9, 47). Although nonabsorbable membranes have been used successfully in animal experiments and in clinical studies, they persist after healing and must be removed in a second operation (47). Bioabsorbable barrier materials for GTR have been introduced in order to avoid a second surgery for membrane removal (47) and based on the results of the current study could be beneficial for endodontic surgery.

Conclusions

Based on the currently available data, GTR techniques may improve the outcome of bone regeneration after surgical endodontic treatment preformed in cases with certain periapical lesions, such as large periapical lesions, and through-and-through lesions. A favorable outcome is expected for using a resorbable membrane over a nonresorbable membrane or a graft alone. Large-scale prospective clinical studies are needed to further evaluate possible benefits of GTR techniques in endodontic surgery.

Acknowledgments

The authors deny any conflicts of interest related to this study.

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