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Guided Tissue Regeneration Using a Barrier Membrane in Endodontic Surgery

A Comprehensive Review

KEYWORDS

Endodontic surgery,
 apicoectomy,
 guided bone regeneration

SUMMARY

Endodontic surgery aims at the resolution of a periapical inflammatory process by surgical access followed by enucleation of the lesion and root-end filling to curb any potentially noxious agent within the physical confines of the affected root. Guided bone regeneration could be associated to endodontic surgery aiming to enhance periradicular tissue regeneration.

The objective of this paper was to review the scientific literature about guided bone regeneration in endodontic surgery, evaluating the effects on periapical lesion healing process. The included

articles are classified considering the anatomical characteristics of the lesion.

Fourteen articles were included in the review after abstract and title selection. Eight articles were on studies on lesions affecting only the periapical region (three about through-and-through lesions) while six were about the treatment of apico-marginal lesions.

On the basis of the currently available literature, there is a low scientific evidence of a benefit related to the use of guided bone regeneration procedure in endodontic surgery.

Introduction

Guided tissue regeneration (GTR) techniques have been widely used for bone and periodontal tissue regeneration. In endodontic surgery, GTR has been applied using different bone substitute materials and/or different barrier membranes. The concept of GTR was introduced first by the Lindhe group (NYMAN ET AL. 1982). The principles of GTR are based on the concept that if epithelial cells, that migrate approximately ten times faster than other periodontal cell types (ENGLER ET AL. 1966) are excluded from the wound space long enough for other cell types (as osteoblasts) with regenerative potential to become established, epithelial downgrowth is prevented and regeneration can be achieved. This can be obtained by using various barrier membranes with or without bone grafts. The objectives of the application of a “space making technique” in

endodontic surgery resemble those in periodontology and implantology: (i) facilitate tissue regeneration by creating an optimum environment (stable and protected wound); and (ii) exclude non-desired fast proliferating cells from interfering with tissue regeneration.

Among prognostic tooth-related factors that may influence the healing rate in endodontic surgery are the extent and location of periradicular bone loss (RUD ET AL. 1972, HIRSCH ET AL. 1979, GUTMANN & HARRISON 1991). It was reported that a delay or alteration of healing might occur when the lesion size was greater than 5mm (STORMS 1969, RUD ET AL. 1972, TAY ET AL. 1978). Moreover, several authors showed that the prognosis of endodontic surgery is better with smaller than in larger lesions (RUD & ANDREASEN 1972, FINNE ET AL. 1977, HIRSCH ET AL. 1979, SKOGLUND & PERSSON 1985, MOLVEN ET AL. 1987). RUBINSTEIN & KIM (1999) ob-

served that small lesions (0–5 mm) and those of medium size (6–10 mm) healed within 7.25 months, and lesions larger than 10 mm healed within 11 months. In contrast, some authors have suggested that the size of the preoperative lesion has no influence on the ultimate healing of the periradicular defect (NORDENRAM & SVÄRDSTRÖM 1970, LEHTINEN & AITASALO 1972). In another report RUD ET AL. (1972) observed that tooth location and extent of cortical bone loss may have a significant effect on the healing pattern. Moreover, two retrospective studies indicated that the prognosis was substantially worse in teeth with a total loss of the buccal bone plate (HIRSCH ET AL. 1979, SKOGLUND & PERSSON 1985).

It should also be emphasized that combined endodontic-periodontal lesions present a clinical dilemma to the clinician and are challenging as the endodontic and periodontal tissues share an embryologic, biologic and functional interrelation. In fact, endodontic infection may influence the progression of marginal bone loss in periodontitis (FORSSELL ET AL. 1988). It was observed that teeth with periapical radiolucencies have approximately 2 mm less radiographic attachment in comparison to teeth without such lesions (JANSSON ET AL. 1993A). Moreover, a threefold greater rate of marginal radiographic bone loss was reported in teeth of periodontitis-prone patients with an endodontic infection compared to teeth without an infection (0.19 mm/year vs. 0.06 mm/year respectively) (JANSSON ET AL. 1993B, JANSSON ET AL. 1995).

VON ARX & COCHRAN (2001) proposed a classification of bone defects associated with endodontic surgical cases. The same authors identified membrane application techniques based on typical periradicular lesions classified by their location, extension or pathway of infection. Another classification by DIETRICH ET AL. (2002) proposed a subdivision on the basis of pathogenetic and morphologic criteria of perio-endo lesions.

The objective of the present article was to provide an updated review of the literature with regard to GTR application in endodontic surgery and to identify key issues for future research that may improve the knowledge of tissue regeneration in periapical surgery.

Materials and methods

Search strategy

The search covered all articles published in dental journals in English from January 2000 to December 2013. The following electronic databases were searched: MEDLINE, SCOPUS and

EMBASE 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 “membrane” (Tab. I).

In addition, a manual search was performed of articles in reference lists of selected articles and of the following journals: British Journal of Oral and Maxillofacial Surgery, Dental Clinics of North America, Journal of Oral and Maxillofacial Surgery, International Journal of Periodontics and Restorative Dentistry, Journal of Cranio-Maxillofacial Surgery, International Journal of Oral and Maxillofacial Surgery, Journal of Periodontology, Journal of Prosthetic Dentistry, Oral and Maxillofacial Surgery, Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontology, Journal of Endodontics and International Endodontic Journal. Grey literature (abstracts and congress proceedings) was also searched for pertinent articles.

Study selection criteria

This review included animal and human studies that reported the outcome of guided tissue regeneration with barrier membranes in endodontic surgery.

The inclusion criteria were: (1) prospective clinical trials in humans or animals; (2) treatment of periradicular lesions with or without a concomitant periodontal lesion; (3) utilization of a membrane (GTR procedure); (4) articles published from January 2000 to December 2013.

The exclusion criteria were: (1) studies not using membranes; (2) case reports and case series; (3) review articles; (4) retrospective studies; (5) studies without a sufficient description of the treated defects to classify them.

Data collection process

The titles and abstracts of retrieved articles were screened independently by two reviewers (AK and SC) to identify publications that met the inclusion criteria. When the title and abstract of an article did not provide sufficient information to make a decision, the full text was obtained and evaluated. In case of disagreement, a third reviewer (ST) was consulted to finalize the decision after discussion. The full text of all included articles was obtained. Characteristics of the included studies were examined by the reviewers and relevant data were extracted. Studies were categorized according to the classification by VON ARX & COCHRAN (2001) and DIETRICH ET AL. (2002) as presented in Table II.

Tab. I Search strategy per database

DATABASE	SEARCH STRATEGY
PubMed	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 “membrane” Filters: English; publication date from 2000/01/01 to 2013/12/31.
Scopus	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 “membrane” AND (LIMIT-TO(DOCTYPE, “ar”)) AND (LIMIT-TO(SUBJAREA, “DENT”)) AND (LIMIT-TO(LANGUAGE, “English”)) AND (LIMIT-TO(PUBYEAR, 2013) OR LIMIT-TO(PUBYEAR, 2012) OR LIMIT-TO(PUBYEAR, 2011) OR LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR, 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-TO(PUBYEAR, 2005) OR LIMIT-TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003) OR LIMIT-TO(PUBYEAR, 2002) OR LIMIT-TO(PUBYEAR, 2001) OR LIMIT-TO(PUBYEAR, 2000)).
Embase	‘Endodontic surgery’/exp OR ‘apicectomy’ OR ‘apicoectomy’/exp OR ‘periradicular surgery’ OR ‘apical surgery’ OR ‘periapical surgery’ OR ‘root-end surgery’ OR ‘root-end resection’ AND ‘membrane’/exp AND [article]/lim AND [English]/lim AND [2000–2013]/py.

Tab. II Classification of defects in surgical endodontics		
Localization and characteristics of the defect	Classification by VON ARX & COCHRAN (2001)	Classification by DIETRICH (2002)
Bone defect confined to periapical region	Class I	
	Lingual/palatal cortex not eroded	Class I a
	Lingual/palatal cortex eroded (through-and-through bone defect)	Class I b
Apico-marginal lesion	Class II	Class I Class I/1: purely periodontal Class I/2: combined periodontal-endodontic Class I/3: purely endodontic Presence (Class IA) or absence (Class IB) of a bony bridge above the defect after surgery Class II Periapical lesion of purely endodontic origin and characterized by preoperative periodontal probing depths within the normal range. Usually with a fistula close to the gingival margin. Presence (Class IIA) or absence (Class IIB) of a bony bridge above the defect after surgery Class III Apical defect with bony dehiscence (etiology is not infectious).
	Periapical and concomitant marginal lesions without communication	Class II a
	Periapical and concomitant marginal lesions with communication	Class II b
Lateral juxtaradicular lesion	Class III	
	Without communication to marginal lesion	Class III a
	With communication to marginal lesion	Class III b

Data items

The assessment of bone healing and regeneration was based on radiographic and clinical parameters in clinical studies (RUD & ANDREASEN 1972, MOLVEN ET AL. 1987), and on histologic or histomorphometric parameters in experimental studies.

Assessment of risk of bias in individual studies

The risk of bias assessment of the included studies was performed independently by two reviewers (SC and AK), while extracting the data. Criteria for assessing the risk of bias in the present review were: study design, number of examined teeth, follow-up period, method of evaluation, completeness of data reporting and clear specification of success criteria. Risk of bias was judged either low, moderate, or high.

When the study design was a randomized controlled trial the risk of bias was low and when it was a non-randomized controlled trial the risk of bias was judged moderate. In any other case the study was considered as high risk.

With regard to the number of treated teeth in human studies a study was considered as low risk of bias if a sample size calcu-

lation was performed and the number of teeth in groups were comparable at baseline (no more than 5% difference); if the number of teeth in groups were comparable at baseline (no more than 5% difference) but no sample size calculation was performed the study was considered as moderate risk. In any other case the study was considered as high risk. In experimental animal studies if a sample size calculation was performed the study was judged as low risk of bias. In any other case the study was considered as moderate risk.

Considering the risk of bias related to the follow-up period, if the examination lasted at least six months after treatment the study was judged as low risk, if it lasted between three and six months the study was considered as moderate risk, otherwise it was considered as high risk.

With regard to the method of assessment, if the study was evaluated by blind operators using objective parameters (such as numerical evaluation of radiographs or histomorphometric analysis) it was considered as low risk; if one of the described conditions was missing the study was considered as moderate risk, else it was judged as high risk.

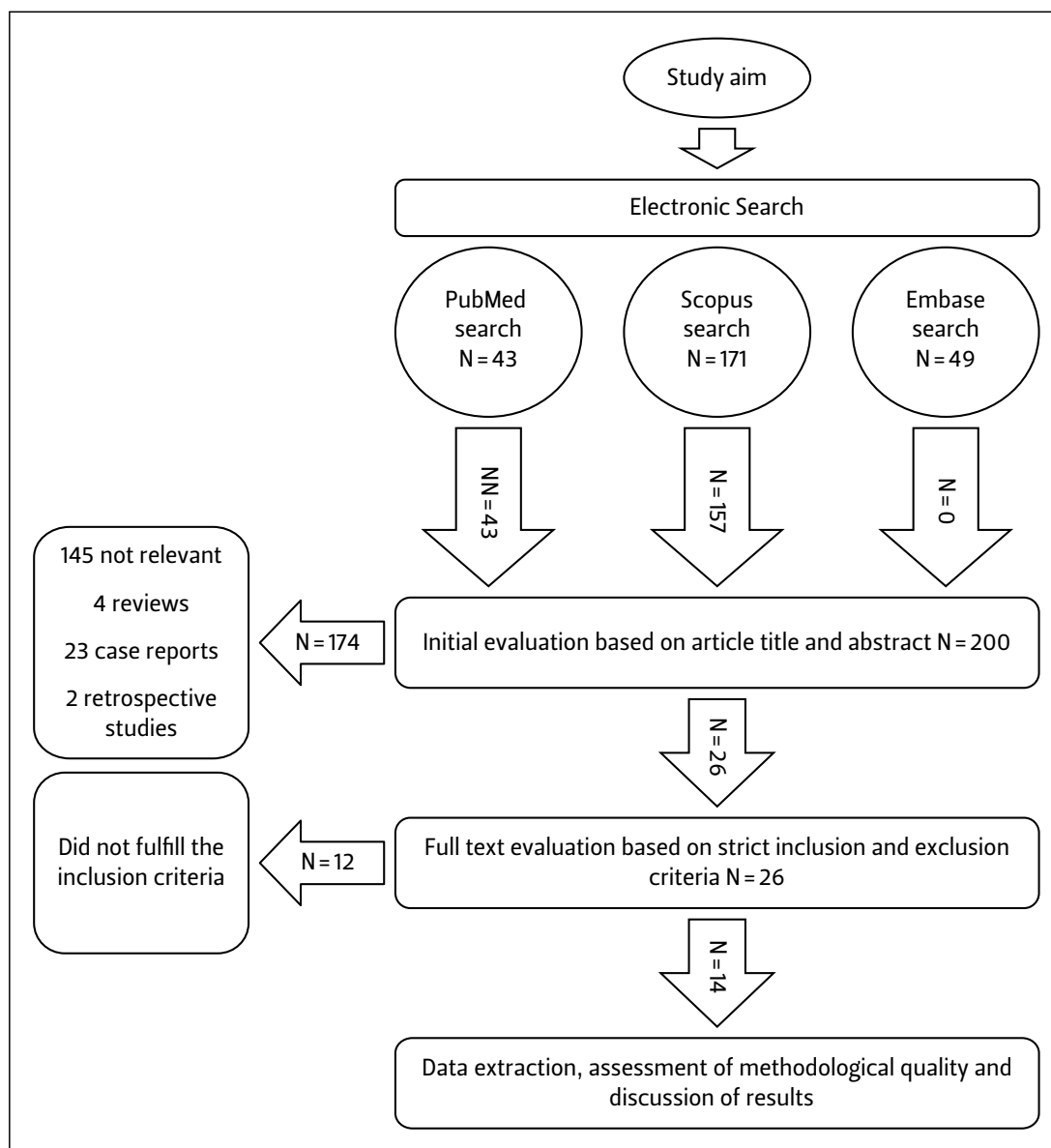


Fig. 1 Flowchart of article selection process

If individual data were presented for any follow-up visit, the study was considered as low risk with regard to completeness of data reporting. If individual data were not reported and results were described as mean and standard deviations the study was judged as moderate risk. In any other case the study was considered as high risk.

When authors presented a clear specification of outcome measures and success criteria the study was judged low risk. If a specification was provided but it was based on subjective interpretation the study was judged moderate risk, else the risk of bias related to this item was considered as high.

To summarize the validity of studies, they were grouped into the following categories: 1) a low risk of bias if none of the quality criteria were judged as high risk and no more than two of them were judged as moderate; 2) moderate risk of bias if one to three criteria were judged as high risk or more than two parameters were judged as moderate; and 3) a high risk of bias if four or more criteria were judged as high risk. In case of discrepancy between the two reviewers, an agreement was obtained after joint discussion. Otherwise, a third reviewer (ST) was consulted to achieve a consensus.

Results

Study selection

The initial electronic search provided 263 studies. Figure 1 is a flowchart of the article selection process. After screening the titles and abstracts, 26 studies were subjected to full text evaluation. Following full text evaluation, 12 articles were excluded (Tab. III). Fourteen articles were subjected to data extraction, quality assessment of methodology, and data analysis. All these articles were summarized and classified according to VON ARX & COCHRAN (2001) and DIETRICH ET AL. (2002).

Risk of bias

A description of the risk of bias of the included studies is summarized in Table IV.

All studies were judged “low risk of bias” except one (DIETRICH ET AL. 2003) that was judged “moderate risk of bias” because of a non-comparative study design.

Results of individual studies

A description of the included studies is presented in Tables V–VIII.

Tab. III Studies excluded from review and exclusion criteria

Study	Exclusion criterion
TASCHIERI ET AL. 2013	No membrane was applied
DEL FABBRO ET AL. 2012	No membrane was applied
MALI R ET AL. 2011	Case report
VAISHNAVI C ET AL. 2011	No membrane was applied
LIN ET AL. 2010	Review article
SAUNDERS ET AL. 2008	GTR was not included as part of the surgical protocol
VON ARX ET AL. 2007	GTR was not included as part of the surgical protocol
BERGENHOLTZ ET AL. 2006	No membrane was applied
APAYDIN AND TORABINEJAD ET AL. 2004	No membrane was applied
MURASHIMA ET AL. 2002	No membrane was applied
PECORA ET AL. 2001	No membrane was applied
DOMINIAC ET AL. 2009	Unclear definition of bony defect

Membrane application in class I lesions

The application of a membrane technique in class Ia lesions has been investigated to date in three experimental animal studies (Tab. V).

In one experimental study in cats, periapical lesions were induced by exposing the root canals of maxillary premolars to the oral flora (ARTZI ET AL. 2012). Six weeks later, endodontic treatment with canal obturation was performed. Root ends were resected and retrograde cavities were filled with IRM® (Dentsply International, York, PA, United States). After 3 months, the amount of bone formation that was evaluated through histomorphometric analysis was slightly greater in the grafted membrane-protected sites ($25.5 \pm 4.8\%$) than in the control sites ($25.0 \pm 16.2\%$). After 6 months, the bone area fraction in protected graft sites ($30.2 \pm 5.7\%$) was comparable to that in the control sites ($30.0 \pm 17.3\%$). Interestingly, the study suggested that the key factor for enhanced tissue regeneration was the presence of a membrane rather than the presence of a bone substitute.

Another study evaluated periapical lesions induced in dogs' teeth (BERNABÉ ET AL. 2010). Ninety days later, endodontic orthograde root canal obturation was performed. Root ends were resected and retrograde cavities were filled with MTA. The authors concluded that the use of a membrane, bone graft, or their combination did not influence the healing process of the root end of periapical lesions.

Tab. IV Assessment of risk of bias

Authors	Year	Study type	Risk of bias evaluation					
			Study design	N° of examined teeth	Follow-up period	Method of assessment	Completeness of data reporting	Clear specification of success criteria
Human studies								
TOBON ET AL.	2001	RCT	Low	High	Low	Low	Low	Low
GARRETT ET AL.	2002	RCT	Low	High	Low	Low	Moderate	Low
DIETRICH ET AL.	2003	Clinical study	High	N/A	Low	Low	Moderate	Low
MARIN-BOTERO ET AL.	2006	RCT	Low	Moderate	Low	Low	Low	Low
TASCHIERI ET AL.	2007	RCT	Low	High	Low	Moderate	Moderate	Low
TASCHIERI ET AL.	2008	RCT	Low	High	Low	Moderate	Moderate	Low
GOYAL ET AL.	2011	Comparative study	Moderate	Low	Low	Moderate	Moderate	Low
Animal studies								
BAEK AND KIM ET AL.	2001	RCT	Low	Moderate	Moderate	Low	Moderate	Low
DOUTHITT ET AL.	2001	RCT	Low	Moderate	Low	Low	Moderate	Low
YOSHIKAWA ET AL.	2002	RCT	Low	Moderate	Low	Low	Moderate	Low
VON ARX ET AL.	2003	RCT	Low	Moderate	Low	Low	Moderate	Low
BRITAIN ET AL.	2005	RCT	Low	Moderate	Low	Low	Moderate	Low
BERNABÉ ET AL.	2010	RCT	Low	Moderate	Low	Moderate	Moderate	Low
ARTZI ET AL.	2012	RCT	Low	Moderate	Low	Low	Low	Low

RCT = randomized controlled trial; N/A = not assessable

Tab. V Four animal studies with membrane application in class I lesions

Author(s)	Year	Study design	Animals; number of treated teeth per group (teeth type)	Lesion type	Treatment type	Follow-up	Outcome
ARTZI ET AL.	2012	Experimental (randomized)	Cats; 9 (maxillary first and second pre-molars of each side)	Class I a	Test 1: ABBM (Cerabone® – botiss dental GmbH, Berlin, Germany) Test 2: ABBM (Cerabone® – botiss dental GmbH, Berlin, Germany) and collagen membrane (Osseoguard® – BIOMET 3i, Palm Beach Gardens, FL, United States) Test 3: collagen membrane only (Osseoguard® – BIOMET 3i, Palm Beach Gardens, FL, United States) Test 4: control	3 and 6 months	After 3 months, bone formation was greater at the grafted membrane-protected sites (25.5%) than in the grafted unprotected sites (14.0%). After 6 months, the bone area fraction at membrane non-grafted sites (38.7%) was greater than in the graft-protected sites (30.2%)
BERNABÉ ET AL.	2010	Experimental, comparative (no randomization)	Dogs; 6 (mandibular second and third pre-molars of each side)	Class I a	Test 1: ABBM (GenOx® – Baumer S/A, Mogi Mirim, SP, Brazil) Test 2: ABBM (GenOx® – Baumer S/A, Mogi Mirim, SP, Brazil) and bovine cortical membrane (GenDerm® – Genius Pharma Ltd) Test 3: bovine cortical membrane (GenDerm® – Genius Pharma Ltd) Test 4: control	6 months	No statistical difference among the experimental groups ($P > .05$). The use of membrane, bone graft, or their association did not influence the healing process of the root end of dogs' teeth filled with MTA.
YOSHIKAWA ET AL.	2002	Experimental (randomized)	Dogs; 12 (mandibular third and fourth pre-molars of each side)	Class I a	Test 1: ePTFE membrane (Gore-Tex) Test 2: PLGA membrane Test 3: collagen membrane Test 4: calcium sulfate Test 5: control	4, 8 and 16 weeks (each with four dogs)	Results after 16 weeks (buccal cortical bone regeneration): Test 1: 54.8% Test 2: 21.2% Test 3: 34.0% Test 4: 48.9% Control: 37.4% Test 1 better than Test 2 ($p < 0.01$); Test 3 ($p < 0.05$) and control ($p < 0.05$); Test 4 better than Test 2 ($p < 0.01$) and control ($p < 0.05$)
BAEK AND KIM ET AL.	2001	Experimental	Ferrets; 8 (mandibular premolars)	Class I b (through-and-through lesions)	Test 1: ePTFE membrane (GoreTex®) buccally and lingually Test 2: Polyglactin 910 (PGLA) membrane (Vicryl® – Ethicon Endo-Surgery Inc., Cincinnati, OH, United States) buccally and lingually Test 3: polylactide membrane (Guidor® – Sunstar, Chicago, IL, United States) buccally and lingually Test 4: control	Two sub-groups of healing: 6 weeks and 12 weeks	Histology at 12 weeks: Test 1: defects were filled with regenerated immature bone, Test 2: defects showed extensive lamellar bone healing, Test 3: only limited fibered bone regeneration, control: connective tissue infiltration Radiography (%) of tissue regeneration after 12 weeks: Test 1: 95%, Test 2: 95%, Test 3: 90%, control: 80%

ABBM = anorganic bovine bone mineral; ePTFE = expanded polytetrafluoroethylene; PLGA = polylactic-co-glycolic-acid

The third experimental study evaluated bone regeneration of the buccal cortical wall in osseous defects after endodontic surgery in dogs (YOSHIKAWA ET AL. 2002). Endodontic surgery was performed on the mandibular premolars on both sides after root canal treatment and retrograde cavities were filled with Super-EBATM (Bosworth Company, Skokie, IL, United States). The histological findings 16 weeks after surgery showed that e-PTFE membranes were more effective (54.8%) compared to resorbable membranes (21.2% and 34.0%) and controls (37.4%) with regard to the regeneration of the cortical bone plate after endodontic surgery. Also calcium sulfate (48.9%) was found superior to resorbable membranes and controls.

The application of a membrane technique in Class Ia lesions has been investigated to date in two clinical studies (Tab. VI).

One clinical study investigated the rate of healing of periapical bone defects (Class Ia) after endodontic surgery (GARRETT ET AL. 2002). After one year, the study showed that there was no statistical difference between the membrane-treated and the control groups ($p = 0.6133$). The results demonstrated that placement of a barrier membrane over the bony opening created during an endodontic surgical procedure had no benefi-

cial effect on the rate of healing and the added expense to the patient would not be warranted in those cases.

Another clinical study aimed at evaluating two materials for bone regeneration during endodontic surgery and their effects on healing in 28 patients (TOBON ET AL. 2002). One year postoperatively, 44% of complete healing was observed in the negative control group, 67% of complete healing in the group treated with a barrier membrane while complete healing was observed in all cases treated with a barrier membrane and a bone graft. The application of a membrane technique in class Ib lesions (through-and-through lesions) has been investigated to date in one animal and in two clinical studies (Tab. V and VI).

An experimental study was performed in the mandibular premolars after root canal treatment and bilateral creation of oval through-and-through osseous defects at the level of the root apices (Class Ib) (BAEK & KIM 2001). The histological findings 12 weeks after surgery showed that membrane barriers placed over through-and-through bone defects generally improved bone regeneration.

A clinical study investigated the success rate of endodontic surgery with or without the adjunct of anorganic bovine bone

Tab. VI Four human studies with membrane application in class I lesions

Author(s)	Year	Study design	N° of subjects (test/control)	Lesion type	Treatment type	Follow-up	Outcome
GARRETT ET AL.	2002	Randomized clinical trial	25/13	Class Ia	Test: polylactide membrane (Guidor® – Sunstar, Chicago, IL, United States) Control: no membrane	3, 6 and 12 months	Test 3 m: 89%, Test 6 m: 94%, Test 12 m: 97%, Control 3 m: 82%, Control 6 m: 97%, Control 12 m: 91% ($p > 0.05$)
TOBON ET AL.	2002	Randomized clinical trial	28/25; number of treated teeth 30/26	Class Ia	Test 1: ePTFE membrane (Gore-Tex®) Test 2: resorbable hydroxyapatite (OsteoGen® – Osteogen, Sao Paulo, SP, Brazil) and ePTFE membrane (Gore-Tex®) Control: neither grafts nor membranes were used.	12 months	Test 1: 62.5% trabecular bone 66.66% complete healing 11.11% incomplete healing Test 2: 100% trabecular bone 100% complete healing Control: 25% trabecular bone 44.44% complete healing 44.44% incomplete healing
TASCHIERI ET AL.	2008	Randomized clinical trial	27/25; number of treated teeth 34/31	Class Ib (through-and-through lesions)	Test: ABBM (Bio-Oss® – Geistlich Pharma AG, Wolhusen, Switzerland) and Collagen membrane (Bio-Gide® – Geistlich Pharma AG, Wolhusen, Switzerland) buccally only Control: neither grafts nor membranes were used.	12 months	Test: 88.0%, Control: 57.1% ($p = 0.02$)
TASCHIERI ET AL.	2007	Randomized clinical trial	44/41; number of treated teeth 63/59	Class Ib (through-and-through lesions)	Test: ABBM (Bio-Oss® – Geistlich Pharma AG, Wolhusen, Switzerland) and Collagen membrane (Bio-Gide® – Geistlich Pharma AG, Wolhusen, Switzerland) buccally only Control: neither grafts nor membranes were used.	12 months	Test: 83.3%, Control: 74.3% ($P = .09$)

ABBM = anorganic bovine bone mineral; ePTFE = expanded polytetrafluoroethylene

and a resorbable membrane for the treatment of periapical through-and-through lesions (TASCHIERI ET AL. 2008). One year after surgery, the test group showed better outcome (88% success) than the control group (57% success).

Another clinical study investigated the success rate of endodontic surgery in patients with large periapical lesions (≥ 10 mm) with or without anorganic bovine bone in conjunction with a resorbable membrane (TASCHIERI ET AL. 2007). One year postoperatively, no statistically significant difference was found comparing cases treated with GTR (83.3% success) and without GTR (74.3% success) ($P = .09$). The results suggested that the combined use of membrane and bovine bone matrix

in large periapical lesions had no beneficial effects on the rate of bone healing even for treatment of large lesions.

Membrane application in class II lesions

The application of a barrier membrane in class II lesions has been investigated to date in three animal studies (Tab. VII).

In one experimental study, periapical lesions were induced by exposing the root canals followed by removal of cortical bone over the roots (BRITAIN ET AL. 2005). Six weeks later, endodontic treatment with canal obturation was performed. Root ends were resected and retrograde cavities were filled with MTA. Three different treatment conditions were analysed. Clinical,

Tab. VII Three animal studies with membrane application in class II lesions

Author(s)	Year	Study design	Number of treated teeth test/control (teeth type)	Lesion type	Treatment type	Follow-up	Outcome
BRITAIN ET AL. (*)	2005	Experimental (non-randomized)	4/4 (mandibular premolars #2-4)	Class II b	Test 1: collagen membrane (Bio-Gide® – Geistlich Pharma AG, Wolhusen, Switzerland) Test 2: ABBM (Bio-Oss® – Geistlich Pharma AG, Wolhusen, Germany) and collagen membrane (Bio-Gide® – Geistlich Pharma AG, Wolhusen, Switzerland) Control: open flap debridement	6 months	Test 1 and Test 2 resulted in increased amounts of buccal bone (3.24 mm and 3.45 mm respectively) compared to the control (2.16 mm). Statistically significant increase in the amount of new cementum was also observed in Test 1 and Test 2 when compared with control ($P < 0.05$).
VON ARX ET AL. (*)	2003	Experimental (non-randomized)	4/4 (mandibular premolars #2-4)	Class II b	Test 1: collagen membrane (Bio-Gide® – Geistlich Pharma AG, Wolhusen, Switzerland) Test 2: ABBM (Bio-Oss® – Geistlich Pharma AG, Wolhusen, Switzerland) and collagen membrane (Bio-Gide® – Geistlich Pharma AG, Wolhusen, Switzerland) Control: open flap debridement	6 months	Percentage of new bone formation of control: 36.8% Test 1: 42.3% that did not differ significantly ($P > .90$); however, Test 2: 19.1% had a significantly ($P < .005$) lower mean percentage of new bone formation (with 28.5% of remaining filler particles) compared to the other two test groups
DOUTHITT ET AL.	2001	Experimental (randomized)	9/9 (mandibular premolars #3 and #4)	Class II b	Test: polylactide membrane (Guidor® – Sunstar, Chicago, IL, United States) Control: no membrane	9 weeks and 27 weeks	Histology at 27 weeks: test sites had greater width and height of new bone on the buccal root surface than control sites; an increased length of junctional epithelium was a frequent finding in the control group. Histomorphometry at 27 weeks over denuded root surface: connective tissue attachment: test 4.15 mm, control 1.81 mm ($p < 0.05$); bone: test 2.49 mm, control 0.66 mm ($p < 0.05$). Complete bony fill of periradicular defect: test 89%, control 68.8%

ABBM = anorganic bovine bone mineral; (*): both studies based on the same treated teeth

radiographic and histologic data six months later revealed that using a barrier membrane or a membrane and a bone graft resulted in increased amounts of buccal bone (3.24 mm and 3.45 mm, respectively) compared to open flap debridement only (2.16 mm). Another report from the same experimental study evaluated the amount of new periapical bone formation (VON ARX ET AL. 2003). The authors concluded that membrane application and placement of a bone grafting material did not significantly enhance new bone formation within the apical bone defect.

Another experimental study evaluated histologically the regeneration of the periodontium in the absence of both perira-

dicular bone and buccal cortical bone after the placement of a resorbable membrane in dogs (DOUTHITT ET AL. 2001). Endodontic surgery was performed in teeth using an acute wound model. The study showed that the amount of regenerated alveolar buccal and apical bone was significantly greater in the membrane group, being almost four times that of the negative control group ($p = 0.001$).

The application of a membrane technique in class II lesions has been investigated to date in three clinical studies (Tab. VIII).

One clinical study evaluated the use of platelet-rich plasma (PRP) and collagen membrane (without any bone substitute) for treatment of apicomarginal defects in endodontic surgery

Tab. VIII Three human studies with membrane application in class II lesions

Author(s)	Year	Study design	Human number	Lesion type	Treatment type	Follow-up	Outcome
GOYAL ET AL.	2011	Randomized clinical trial	40/25	Class II b	Test 1: collagen membrane (Healiguide® – EnColl, Newark, CA, United States) Test 2: PRP only Test 3: PRP + collagen sponge	3, 6, 9, 12 months	Success rate in terms of combined clinical–radiographic healing after 12 months; Test 1: 80% Test 2: 83.33% Test 3: 88.89% All the three treatments showed highly significant ($P < .05$) reductions in the periodontal pocket depth (PD), the clinical attachment level (CAL), the gingival margin position (GMP), the size of the periapical lesion, the percentage reduction of the periapical rarefactions, and periapical healing. No significant differences between the three groups were evident for these parameters ($P > .05$).
MARIN-BOTERO ET AL.	2006	Double-blind, randomized clinical trial	67/30	Class II b	Test 1: periosteal graft Test 2: Polyglactin 910 membrane (Vicryl® – Ethicon Endo-Surgery Inc., Cincinnati, OH, United States)	12 months	Reduction of size of periapical lesion after 12 months; Test 1: 91.1% Test 2: 87.0% Clinical–radiographic complete healing after 12 months; Test 1: 60% Test 2: 40% No significant difference between the groups was evident for periodontal PD, CAL parameters, or for the percentage reduction of size of the periapical lesion and clinical–radiographic healing.
DIETRICH ET AL.	2003	Clinical cohort	(24/22) with number of teeth to be treated 25/23	Class II b	ABBMa (Bio-Oss) and collagen membrane (Bio-Gide); no controls	12 months	Successful outcome was 82.6%.

ABBM = anorganic bovine bone mineral; PRP = platelet-rich plasma; PD = periodontal pocket depth; CAL = clinical attachment level

(GOYAL ET AL. 2011). PRP grafts performed similarly to absorbable barrier membranes regarding the reduction of the size of the periapical lesion.

Another clinical study compared the healing response to periosteal sliding grafts and polyglactin 910 periodontal mesh used as barrier membranes (without bone graft) for treatment of apicomarginal defects (MARIN-BOTERO ET AL. 2006). After 12 months both groups showed significant ($P < 0.001$) reductions in periodontal probing depth, clinical attachment loss and size of periapical lesion. No significant difference was found between the experimental groups regarding the percentage reduction of the lesion size and clinical-radiographic healing.

The third clinical study evaluated the periapical and periodontal healing of teeth presenting apicomarginal defects (DIETRICH ET AL. 2003). Guided tissue regeneration using deproteinized bovine bone and a collagen membrane yielded clinically and radiographically good results in terms of periapical and periodontal healing after 12 months.

Discussion

The aim of this review based on experimental and clinical studies was to assess the efficacy and effectiveness of guided tissue regeneration (GTR) in enhancing hard and soft tissue healing after endodontic surgery.

The results of the present comprehensive review demonstrated a substantial heterogeneity among the included studies with regard to study design, surgical technique, barrier membrane, bone graft materials, patient populations and follow-up. As a consequence no meta-analysis could be performed.

As regards the methodology of the review, the chosen inclusion criteria allowed to include only studies in which the description of the treated defects permitted to classify them following the proposed classifications. This could have limited the number of total studies included, but it was functional with respect to the aims of the review. Moreover, it has to be considered that the results from studies on animals could not be completely applicable to humans, due to the peculiar characteristics of animal anatomy and healing processes. This aspect could limit the external validity of the assumptions of the present study.

Endodontic surgery has become a standard of care for tooth maintenance if conventional endodontic retreatment is not feasible or associated with risks. However, in certain situations the outcome of endodontic surgery may be compromised or uncertain due to the extent or location of the periapical or periradicular lesions (VON ARX & ALSAED 2011).

GTR in cases undergoing endodontic surgery for lesions limited to the periapical area (Class Ia)

Most of the included studies did not show a significant beneficial effect of the application of barrier membranes (with or without bone graft) in comparison to negative controls with regard to the amount of bone fill or success rate (TOBON ET AL. 2002, GARRETT ET AL. 2002, BERNABE ET AL. 2010, ARTZI ET AL. 2012). Moreover, the results of animal studies were comparable to those of clinical studies in humans.

By definition, class Ia lesions have intact buccal and lingual bone plates. In order to create the surgical access window for apical surgery, the removal of buccal bone is required resulting in a bone defect with a 4-wall configuration, i.e., with intact mesial, distal, lingual and basal bone structures. Usually, the

grafted and membrane-protected sites resulted in a better outcome when comparing with graft only or membrane only techniques.

Although using a non-resorbable barrier membrane (ePTFE) resulted in better outcome compared to a resorbable barrier membrane in Yoshikawa's study (YOSHIKAWA ET AL. 2002) that evaluated only the regeneration of the buccal cortical bone, the indication for using a non-resorbable membrane remains debatable due to the relatively frequent complications associated with this type of membrane (GHER ET AL. 1994, AUGTHUN ET AL. 1995, MACHTEI 2001). In addition, the ePTFE membrane needs to be removed in a second surgery, increasing cost and patient morbidity. Anorganic bovine bone mineral was the material of choice in most studies. In one study (TOBON ET AL. 2002) the use of a non-resorbable membrane did not provide a higher percentage of bone fill than the use of a resorbable membrane.

In summary, taking into consideration the current data from human and animal studies, GTR in endodontic surgery in this particular kind of lesions did not provide a significant beneficial effect with regard to healing outcome.

GTR in cases undergoing endodontic surgery for through-and-through lesion (Class Ib)

A tunnel (or through-and-through) lesion is characterized by an eroded buccal and lingual bone plate, or the tunnel lesion results after creation of the buccal bony access window in cases with lesions that have eroded only the lingual bony plate. The bony crypt typically has a three-wall configuration with mesial, distal, and basal bone structures but the buccal and lingual bone plates are missing. Since new bone formation is slower compared to soft tissue proliferation, the latter will grow into the "unprotected" bony crypt with a scar bridging the defect from buccal to lingual, thereby preventing or retarding bone formation. The reviewed human and animal studies demonstrate that cases with tunnel lesions may benefit from using GTR, in particular to prevent scar tissue formation. However, only three articles were available. One experimental study on animal model found that resorbable barrier membranes (Vicryl® - Ethicon Endo-Surgery Inc., Cincinnati, OH, United States) displayed a better outcome in comparison to non-resorbable barrier membranes (ePTFE) (BAEK & KIM 2001). Another study used graft material (Bio-Oss® - Geistlich Pharma AG, Wolhusen, Switzerland) covered with a resorbable membrane (Bio-Gide® - Geistlich Pharma AG), which resulted in better outcome in comparison to the negative control group (TASCHIERI ET AL. 2008). Hence, in these cases it is recommended to use a resorbable barrier membrane with or without a graft material on both buccal and lingual aspects of the tunnel lesion in order to prevent the ingrowth of soft tissues allowing faster and greater bone regeneration. Another study by Taschieri and coworkers (TASCHIERI ET AL. 2007) showed that cases with large lesions (>10 mm) did not benefit from using a GTR procedure. However, it may be recommended to place a bone substitute into the bony crypt to support and prevent collapse of buccally and lingually placed non-rigid membranes. Moreover, in that study, it appeared that the difference in percentage of bone fill comparing GTR and negative control group was negligible. In fact, it is known that the lesion size is a major factor influencing the healing rate of periapical lesions, also in cases with orthograde endodontic treatment (RICUCCI ET AL. 2011, TESIS ET AL. 2011).

When considering these results, it should be stated that there was heterogeneity in the materials (membranes and bone sub-

stitutes) used in the included studies, and this could limit the validity of the results. More randomized controlled studies are needed to confirm these results, allowing to understand the usefulness of GTR in the treatment of through-and-through lesions.

GTR in cases undergoing endodontic surgery for apico-marginal lesions (class II lesions)

An apico-marginal lesion is the most challenging situation in endodontic surgery, particularly when the buccal bone plate is completely missing. In some cases a thin facial bone plate is still present but the buccal root surface is exposed. The main problem of an apico-marginal lesion is that healing is often characterized by epithelial downgrowth along the denuded root surface after apical surgery. As a consequence, a long junctional epithelium forms along the root surface with an increased risk of a recurrent communication between marginal and apical tissues (SKOGLUND & PERSSON 1985).

Two of three reviewed animal studies (with control groups) and human studies (without control groups) demonstrated a beneficial effect of barrier membranes (with or without bone filler) with regard to the healing of apico-marginal lesions. The results of the study by Douthitt and colleagues (DOUTHITT ET AL. 2001) differed substantially from those of another study (BRITAIN ET AL. 2005) because of the differences in creating and treating the lesions, showing that the treatment of acute and infected lesions could be much more challenging than the treatment of chronic and non-infected lesions. Although the three reviewed clinical studies did not have a control group (DIETRICH ET AL. 2003, MARIN-BOTERO ET AL. 2006, GOYAL ET AL. 2011), making the judgement of a clinical benefit of using a membrane difficult, it was demonstrated that the application of GTR in apico-marginal defects with bone filler and a bioresorbable collagen membrane might result in good outcomes. The study by Goyal et al. showed that PRP might be an alternative to membrane barriers in the treatment of apico-marginal defects (GOYAL ET AL. 2011). No clinical or experimental study has so far evaluated the use of PRP or enamel matrix derivatives for treatment of apico-marginal lesions in conjunction with endodontic surgery. The clinician is advised to cautiously select cases for apical surgery in teeth with complete denudation of buccal (and/or proximal) root surfaces. In multi-rooted teeth extraction or root/tooth resection should be considered as treatment alternatives.

GTR in cases undergoing endodontic surgery for lateral juxtaradicular lesions (Class III lesions)

For this class of lesions no articles were found in this literature review. In the near future GTR may be one of the most attractive indications for these difficult types of lesions.

Conclusions

Based on the currently available data, there is just a sparse scientific evidence that GTR techniques may improve the outcome of bone regeneration after endodontic surgery of periapical lesions with or without a concomitant periodontal lesion. When a periodontal lesion was present, GTR appeared to allow a greater regeneration of periodontal and bone tissues compared to a negative control, but the evidence of this observation is low.

Large-scale prospective clinical studies are needed to further evaluate possible benefits of GTR techniques in association with endodontic surgery, especially in Class II and Class III lesions, which are the most difficult to treat and warrant the use of the

GTR principle to enhance and facilitate tissue regeneration. Also the use of novel biomaterials as enamel matrix derivatives and platelet concentrates needs to be better evaluated for treatment of apico-marginal lesions in conjunction with endodontic surgery.

Résumé

Introduction

Les techniques de régénération tissulaire guidée (GTR) ont été amplement appliquées à la chirurgie orale dans le but de créer des conditions qui permettent la régénération osseuse. Il a été décrit l'utilisation de nombreux biomatériaux et de diverses membranes.

La chirurgie endodontique a pour objectif la guérison du processus inflammatoire périapical par la création d'un accès chirurgical de l'apex, suivi de l'élimination de la lésion et de l'obturation apicale rétrograde afin d'isoler tous les agents pathogènes potentiels dans la racine affectée.

La régénération osseuse guidée peut être associée à la chirurgie endodontique pour favoriser la régénération du tissu périapical, à la suite de l'énucléation de la lésion et l'obturation radiculaire.

Matériel et méthodes

Cette étude avait pour objectif la révision systématique de la littérature scientifique ayant pour sujet la régénération osseuse guidée en chirurgie endodontique, évaluant les effets sur le processus de guérison de la lésion périapicale.

Une stratégie de recherche a été créée et appliquée à différentes bases de données informatiques. Une recherche manuelle a également été réalisée. Après l'application des critères d'inclusions et d'exclusions, les articles sélectionnés ont été classés en fonction des caractéristiques anatomiques de la lésion périapicale.

Les informations concernant les caractéristiques des défauts osseux et le taux de succès de la procédure chirurgicale utilisée ont été isolées et analysées.

L'évaluation du «risk of bias» a été appliquée pour analyser le niveau d'évidence scientifique des études sélectionnées.

Résultats

Après l'analyse des titres et des résumés, 14 articles ont été insérés dans la révision. Huit d'entre eux concernent uniquement le traitement des lésions localisées au niveau de la région périapicale (trois concernant des lésions communicantes), six autres concernent le traitement de lésions apico-marginales.

Toutes les études, sauf une, ont été jugées comme ayant un «risk of bias» faible.

Parmi les études sur modèle animal analysant le traitement des lésions de Classe I, trois ont démontré l'effet positif de l'utilisation de la GTR, alors qu'aucun effet n'a été observé dans une autre. Deux études cliniques sur quatre ont montré un effet bénéfique de l'application des techniques de GTR, en particulier en évaluant la guérison histologique.

Toutes les études sur animaux qui analysent le traitement des lésions de Classe II ont montré un effet positif de la GTR en ce qui concerne le pourcentage de croissance osseuse. En revanche, deux études cliniques sur trois n'ont enregistré aucun effet significatif sur le même type de lésion (Classe II), en évaluant le succès clinique et radiographique.

Aucune étude sur le traitement des lésions de Classe III n'a été trouvée.

Il a été mis en évidence une certaine hétérogénéité en termes de matériaux et méthodes appliquées, organisation de l'étude et dimension des échantillons entre les différents articles sélectionnés. En conséquence, il a été impossible de réaliser certaines analyses quantitatives.

Discussion

Considérant tous les articles sélectionnés, il n'a pas été possible d'observer un effet significatif de l'application de la technique GTR dans le traitement des lésions périapicales (Classe I ou Classe II selon la classification de von Arx & Cochran), en particulier au moment de l'évaluation clinique. De façon générale, les études sur animaux ont mis en évidence un effet bénéfique en termes de guérison osseuse (évaluée grâce à l'analyse histologique), mais ces résultats doivent être interprétés avec précaution. En conclusion, la littérature scientifique à disposition ne permet pas de démontrer l'influence des techniques de GTR pour obtenir un succès clinique et radiologique dans le traitement des lésions périapicales.

Zusammenfassung

Einleitung

Die Technik der gesteuerten Geweberegeneration («guided tissue regeneration», GTR) dient der Regeneration von Knochen und Parodontalgewebe mittels verschiedener Biomaterialien (Knochenfüller sowie Barriere-Membranen).

Die Anwendung der GTR in der apikalen Chirurgie soll die Voraussetzungen für die Wundheilung der periradikulären Gewebe nach erfolgter Eukleation der Läsion und retrograder Abdichtung der Wurzel optimieren. Die eigentlichen Ziele der apikalen Chirurgie sind die Entfernung des periapikalen pathologischen Prozesses sowie der bakteriedichte Verschluss nach Resektion des Apex, um eine Reinfektion aus dem Pulpakanalsystem zu verhindern.

Material und Methoden

Der Zweck des vorliegenden Artikels ist die systematische Analyse der wissenschaftlichen Literatur über die Anwendung der GTR in der apikalen Chirurgie sowie deren Einfluss auf die Wundheilung. Mittels Suchstrategie wurden verschiedene elektronische Datenbanken durchsucht. Zusätzlich erfolgte eine manuelle Suche nach relevanten Artikeln. Anhand der festgelegten Ein- und Ausschlusskriterien wurden mögliche Publikationen identifiziert und unter Berücksichtigung der anatomischen Lage der periradikulären Defekte klassifiziert. Die Daten

der Defekteigenschaften sowie der Erfolgsraten der chirurgischen Eingriffe wurden extrahiert und analysiert. Zusätzlich wurde ein mögliches Risiko der Befangenheit («risk of bias») jeder eingeschlossenen Studie evaluiert, um deren Evidenzgrad zu bewerten.

Resultate

Insgesamt erfüllten 14 Arbeiten die Einschlusskriterien. In acht Publikationen wurde die Anwendung der GTR bei periapikaler Lage (Klasse I) der Läsion (davon drei Arbeiten mit durchgängigen «tunnelierenden» Läsionen, Klasse Ib) und in sechs Publikationen bei kombinierten apiko-marginalen Läsionen (Klasse II) beschrieben. Mit Ausnahme einer Studie wurden alle Arbeiten mit einem geringen «risk of bias» bewertet.

Bezüglich Anwendung der GTR bei apikaler Chirurgie von Klasse-I-Läsionen zeigten drei (davon eine mit Klasse Ib) von vier Tierstudien einen positiven Effekt auf die Wundheilung. Von vier klinischen Studien bezüglich Klasse-I-Läsionen ergaben zwei Studien (davon eine mit Klasse Ib) eine signifikant bessere Heilung nach GTR-Anwendung, insbesondere unter Berücksichtigung der histologischen Analyse der Gewebeheilung in einer der beiden Studien.

Bei Klasse-II-Läsionen berichteten alle analysierten tierexperimentellen Studien über eine positive Wirkung der GTR mit einem erhöhten Prozentsatz der Knochenneubildung. Hingegen zeigten zwei von drei klinischen Studien bei Klasse-II-Läsionen keinen signifikanten Unterschied bezüglich der Heilung, ob mit oder ohne GTR-Anwendung bei der apikalen Chirurgie.

Diskussion

Studien, welche den Effekt der GTR bei Chirurgie von Klasse-III-Läsionen (laterale Defekte) untersucht hätten, wurden keine gefunden. Insgesamt wurde bei den eingeschlossenen Publikationen eine erhebliche Heterogenität beobachtet bezüglich der verwendeten Materialien und Techniken, Studiendesigns sowie Stichprobengrößen. Als Folge konnte keine Metaanalyse durchgeführt werden.

Allgemein zeigten Tierstudien histologisch einen vorteilhaften Effekt der GTR auf die Knochenheilung – aber diese Ergebnisse müssen mit Vorsicht beurteilt werden. Abschliessend kann festgestellt werden, dass die ausgewertete Literatur nur eine geringe Evidenz für eine erhöhte klinische und/oder radiologische Erfolgsrate nach Anwendung von GTR-Techniken in der apikalen Chirurgie belegt.

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