Original Article

Efficacy of Guided Tissue Regeneration (GTR) Membranes in the Healing of Apico-marginal Defects: A Prospective, Controlled Clinical Trial

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Abstract

Background: There is still inadequate information available regarding the role of GTR techniques in such lesions with the presently available data suggesting that there is a possibility of healing of apico-marginal defects without use of GTR technique by using modern microsurgical procedures. Fewer randomized-clinical trials have evaluated the response of GTR membranes in the treatment of apico-marginal defects. **Aim:** The present prospective, controlled clinical trial was, therefore, planned to evaluate the role of collagen membrane as GTR material in the healing of apico-marginal defects. **Subjects and Methods:** Thirty patients meeting inclusion criteria were selected and allocated randomly to either the GTR membrane group or, the control group. Clinical and radiographic examination was done after one week for baseline measurements and then, during follow-ups at regular intervals of 3, 6, 9, and 12 months after the procedure. The criteria for success included the absence of clinical signs and symptoms and signs of radiographic healing. **Statistical Analysis Used:** The statistical analysis of the ordinal data was carried-out by using non-parametric methods. Mann-Whitney and Wilcoxon signed rank test were used for the unpaired and paired data respectively. Chi-square test was used to evaluate dichotomous data. **Results:** Significant reductions were observed in the periodontal pocket depth (PD), clinical attachment level (CAL), gingival margin position (GMP) and the size of the peri-apical lesion at 12-month follow-up ($P < 0.05$) in each treatment group except gingival margin position (GMP) in the GTR membrane group with the corresponding P value being 0.059. The results for the reduction in the size of the peri-apical lesion were, also, found to be statistically significant with the corresponding P value being <0.05. Furthermore, 83.33% of the patients showed complete healing in case of GTR membrane group while the same was found to be 90.9% in case of the control group although the difference in the percentage reduction in the size of the peri-apical lesion at different time intervals after surgery was found to be statistically insignificant between the two groups. **Conclusion:** The results of the present study indicated that there might not be any additional clinical advantage obtained from GTR membrane barriers in the surgical management of isolated apico-marginal defects of primary endodontic origin with absent or, minimal proximal bone loss.

Keywords: Apico-marginal defects, clinical study, collagen membrane, endodontic microsurgery, guided tissue regeneration

Introduction

Apico-marginal defects, localized bony defects characterised by total deficiency of alveolar bone over the entire root length, have been reported to have lower success rates ranging from 27-37%.[1,2] It is proposed that formation of long junctional epithelium during healing phase over the dehisced root surface may contribute to relatively lower success rates for such lesions.[1,3,4] Successful treatment may, thus, depend not only on the elimination of bacteria from the root canal system but also, on preventing epithelial proliferation along the denuded root surface. Guided tissue regeneration (GTR) techniques with barrier membranes have been proposed as an important adjunct in the management of endodontic-periodontal lesions. Such a membrane, when placed over a bony defect, may prevent the downgrowth of epithelial cells and provide an opportunity for the cells of the periodontal ligament and endosteum to regenerate the lost tissue.[5,6] Literature is replete with case reports and clinical studies which demonstrate high success

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with GTR membranes and advocate their use in apico-marginal defects.[7-19] Very few studies have evaluated the utility of GTR techniques in the healing of apico-marginal defects.[20-22] Some of these have advocated the use of GTR techniques in such lesions, however, they could not find any statistically significant results with the use of the same. Kim E and Song JS, in a prospective clinical study, reported 73.7% success rate by using calcium sulphate and collatape (resorbable collagen membrane) in peri-apical lesions with complete denudement of buccal bone plate (type F lesions) and 63.6% success rate even if no membrane was used for type E lesions.[23] Song M *et al*., also, reported 70.4% success rate in apico-marginal defects without use of any GTR technique.[24] To conclude, there is still inadequate information available regarding the role of GTR techniques in such lesions with the presently available data suggesting that there is a possibility of healing of apico-marginal defects without use of GTR technique by using modern microsurgical procedures. Fewer randomized-clinical trials have evaluated the response of GTR membranes in the treatment of apico-marginal defects.[16,17] The present prospective, controlled clinical trial was, therefore, planned to evaluate the role of collagen membrane as GTR material in the healing of apico-marginal defects.

Subjects and Methods

Subject enrollment and inclusion/exclusion criteria

This clinical trial was conducted after obtaining ethical approval from the Institutional Ethics Board. Forty study subjects were recruited from the pool of patients referred between January 2012 and January 2013. The age of the patients ranged from16 to 47 years. Eligibility criteria included apico-marginal communication confined to buccal aspect with a pocket depth (PD) of >6 mm and recurrent episodes of purulent discharge, teeth with negative response to vitality tests, with radiographic evidence of peri-apical pathoses, failed previous root canal treatment or, re-treatment at least 12-month previously and adequate final restoration with no clinical evidence of coronal leakage. Teeth with vertical root fracture, resorptive processes extending to more than the apical third of the root and subjects with chronic generalized periodontitis, systemic disease contraindicating surgical procedures and conditions affecting healing including diabetes mellitus and smoking were excluded from the study. All the patients were duly informed about the nature of the study, the procedures involved and the associated risks and benefits before obtaining their written consent. The minimum sample size was determined to be 15 patients in each treatment group on the basis of an error of $\alpha = 0.05$ and power at 0.80.

Pre-operative procedures and primary outcome measurements

After obtaining consent, the patients were thoroughly examined and clinical signs and symptoms were recorded carefully. Each patient received full mouth scaling and root planing, and, if needed, occlusal adjustments were carried-out. The patients were, then, recalled after one week for baseline examination. All clinical periodontal measurements were performed by the same investigator (R.R.). The clinical parameters recorded included periodontal pocket depth (PD), clinical attachment level (CAL) and gingival margin position (GMP). Each of these were measured on the buccal aspect of mesial and distal inter-proximal spaces and the mid-buccal aspect of involved teeth (rounded off to the nearest mm) using a Williams O probe. Only the site with the deepest measurement at baseline was taken into consideration. PD was measured from the gingival margin to the base of the defect. The cemento-enamel junction (CEJ) or, the apical border of the restoration, if the CEJ was not visible, was used as a reference for CAL and GMP measurement. Digital intra-oral peri-apical (IOPA) radiographs were taken with Kodak RVG 6000 (Kodak Digital Radiography System, Pt. Husada Intra Care, Indonesia) using the Rinn (XCP Instruments, Elgin, IL) paralleling device after one week for baseline measurements and then, during follow-ups at regular intervals of 3, 6, 9, and 12 months after the procedure. Using CDR DICOM software (Schick CDR Technologies, Long Island City, NY), the digital x-ray images were divided into grid blocks, each with size of 1 mm². Finally, the size of the lesion was calculated by counting the number of blocks with more than 50% area lying in the radiolucent lesion. Subjects were randomly assigned to the GTR membrane group or, the control group without stratification to eliminate any bias. Using an equal proportion allocation technique, sealed envelopes with assigned code were created by another investigator (S.T.) which were, then, utilized for randomization of the subjects in the two given groups. It was further ensured that neither the clinician, nor the patients were aware of the group allocation till the time of placement of membrane.

Procedure for measuring size of peri-apical lesion

Using CDR DICOM software (Schick CDR Technologies, Long Island City, New York), the digital radiographs obtained were divided into blocks with the help of grids [Figure 1]. The dimension of each block of grid was 1mm² eliminating

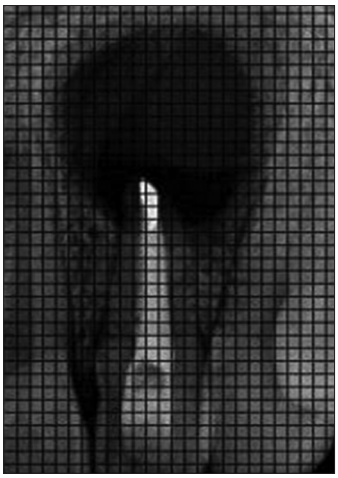


Figure 1: Procedure for measuring size of peri-apical lesion on Digital intra-oral peri-apical (IOPA) radiographs with the help of grids.

those blocks occupying less than 50% of the lesion size while considering those occupying more than 50% of lesion size. Finally, the area of the lesion was calculated by counting the number of blocks. Size of lesion was measured immediately after suture removal and every 3 months up to 12 months. For statistical reasons, the results obtained were, further, dichotomized into successful or, failed cases. The criteria for success included the absence of clinical signs and symptoms and signs of radiographic healing. Criteria for failed cases included those with any clinical signs or, symptoms and/or, radiographic evidence of uncertain or, unsatisfactory healing.

Surgical technique

All surgical procedures except for incision, flap elevation and suturing, were performed under the operating microscope (OPMI PICO; Carl Zeiss, Gottingen, Germany) by the same operator (R.R.). All the clinical procedures were performed using a standard surgical protocol reported in a previous study. [18] In the control group, a full-thickness muco-periosteal flap was raised after achieving adequate anesthesia and osteotomy was performed. After debridement of the pathologic tissue, involved root was resected approximately 3 mm from the apex with a no. 170 tapered fissure bur under copious saline irrigation and hemostasis was achieved using cotton pellets soaked in 0.1% epinephrine (Jackson Lab. (Pvt.) Ltd., Punjab, India). Then, the entire area of dehiscence along with the resected root surfaces was stained with methylene blue and inspected with micro-mirrors (Hu-Friedy, Chicago, IL) under a high magnification of 26X to identify isthmuses, fins and other anatomic details of consequence. Root-end preparation with an approximate depth of 3 mm was made with S12-7D ultrasonic retrotips (Satelec) using a piezoelectric ultrasonic unit (P5 Booster, Suprasson Newtron; Acteon Inc, Mt. Laurel, NJ, USA). After ensuring the cleanness of the preparation, root-end filling was done with mineral trioxide aggregate (Pro Root; Retroplast Trading, Rorvig, Denmark) [Figure 2]. In the GTR membrane group, a bio-resorbable collagen membrane (Healiguide, Advanced Biotech Products (P) Ltd., Encoll Corp., Fremont, CA, USA) was placed over the apico-marginal defect, covering 2-3 mm of the healthy bone around all the margins. Flap was carefully repositioned and then, sutured with non-absorbable 4-0 monofilament sutures. Traditional wound compression was avoided in GTR membrane group to prevent collapse of the membrane [Figure 3]. Post-operatively, the patients were instructed to rinse mouth twice daily with a 0.2% chlorhexidine gluconate solution (Hexidine; ICPA health products ltd, India) for plaque control up to 10 days after surgery. The patients were recalled after a week for removal of sutures at the time of which the healing of the surgical site was checked and recorded.

Outcome assessment

The radiographic examination was carried-out every 3 months up to the period of 12 months using the same exposure parameters at baseline. Clinical evaluation was, also, done at the said intervals to look for any signs of failure. However, PD, CAL, and GMP were not measured until 12 months. Follow-up radiographs were compared with baseline radiographs taken prior to the procedure independently by two examiners (P.S., S.M.) blinded to the group to which they belonged. Radiographic healing was designated as complete, incomplete, uncertain, or, unsatisfactory according to the criteria used by Rud *et al*.[25] and Molven *et al*.[26] The category was confirmed for data entry only when two examiners agreed on the same healing category. In case of discrepancy, the examiners sat together and discussed to arrive at a consensus.

Statistical analysis used

Statistical analysis was performed with SPSS (version 13, SPSS Inc., Chicago, USA) package. Data was presented as mean ± standard deviation. Statistical tests performed were two-tailed and interpreted at 5% significance level. The statistical analysis of the ordinal data was carried-out by using non-parametric methods. Mann-Whitney and Wilcoxon

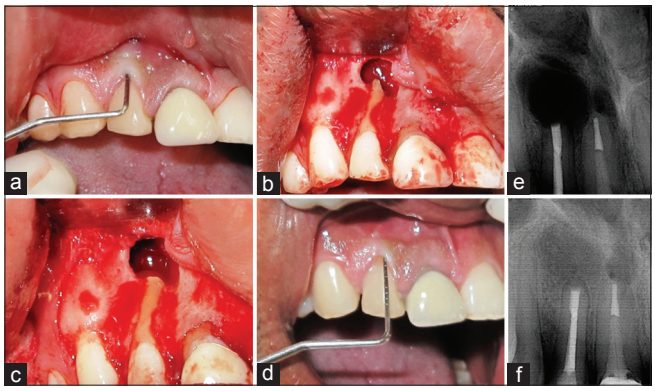


Figure 2: In control group: (a) The pre-operative probing depth. (b) The apico-marginal defect evident after flap reflection. (c) Root resection and apical curettage. (d) The post-operative probing depth at 12-month follow-up. (e) The post-operative radiograph at baseline. (f) The post-operative radiograph at 12-month follow-up showing complete resolution of the peri-apical radiolucency.

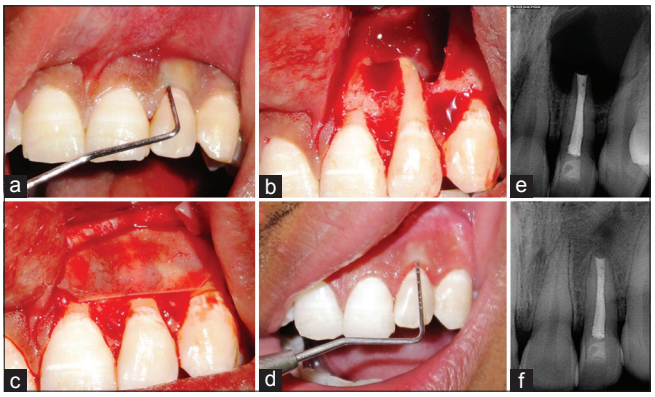


Figure 3: In GTR membrane group: (a) The pre-operative probing depth. (b) The apico-marginal defect evident after flap reflection. (c) Placement of GTR membrane. (d) The post-operative probing depth at 12-month follow-up. (e) The post-operative radiograph at baseline. (f) The post-operative radiograph at 12-month follow-up showing complete resolution of the peri-apical radiolucency.

signed rank test were used for the unpaired and paired data respectively. Chi-square test was used to evaluate dichotomous data. The inter-observer reliability was analyzed with the Cohen kappa analysis. The Cohen Kappa value came-out to be 0.66 which showed that the agreement between the 2 observers was significantly high.

Results

Among the 40 patients included in this clinical trial, 10 patients were excluded before the surgical procedure was carried-out because they did not fulfill the inclusion criteria. Furthermore, a total of 23 patients were examined after 12 months as 7 patients were lost during follow-up, 3 in the GTR membrane group and 4 in the control group because of poor patient compliance. On analyzing the results with the clinico-radiographic parameters at baseline and at 12-month follow-up after surgery in the GTR membrane and control groups, significant reductions were observed in the periodontal pocket depth (PD), clinical attachment level (CAL), gingival margin position (GMP) and the size of the peri-apical lesion at 12-month follow-up ($P < 0.05$) in each treatment group except gingival margin position (GMP) in the GTR membrane group with the corresponding P value being 0.059. The corresponding values at baseline and after 12 months post-surgical procedure were 8.91 ± 1.67 and 1.16 ± 0.38 in the GTR membrane group while 9.00 ± 0.77 and 1.36 ± 0.50 for periodontal pocket depth (PD) in the control group, 9.41 ± 1.97 and 2.08 ± 1.78 in the GTR membrane group while 9.18 ± 1.16 and 2.18 ± 1.32 respectively for clinical attachment level (CAL) in the control group and -0.50 ± 1.44 and -0.91 ± 1.78 in the GTR membrane group while -0.18 ± 0.75 and -0.81 ± 1.07 for gingival margin position (GMP) in the control groups respectively [Table 1]. Wilcoxon signed rank test comparing the reduction in the size of peri-apical radiolucencies at baseline and after 12 months post-surgical procedure revealed a significant reduction in the size of peri-apical radiolucencies at 12 months follow-up in both the groups ($P < 0.05$) with the corresponding values being 133.58 ± 60.94 and 5.00 ± 7.39 at baseline and then, 12-month follow-up in the GTR membrane group while 166.62 ± 177.52 and 19.75 ± 32.27 respectively in the control group [Table 2 and Graph 1] while Mann-Whitney test comparing the percentage reduction in the size of peri-apical radiolucencies between the groups at baseline and after 3, 6, 9 and 12 months post-surgical procedure revealed no significant difference between both the groups at any time given interval ($P > 0.05$) [Table 3 and Graph 2]. Furthermore, 83.33% of the patients showed complete healing in case of GTR membrane group while the same was found to be 87.5% in case of the control group. A case of incomplete healing was noted in the control group while one case each in the category of uncertain and unsatisfactory healing was found in the GTR membrane group [Table 4].

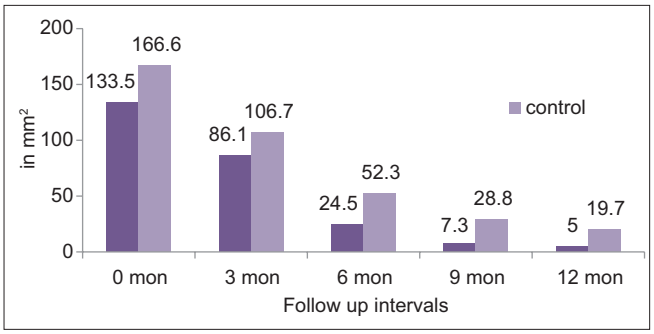
Discussion

Peri-apical pathoses associated with apico-marginal defects pose a complex challenge in endodontic surgery, typically associated with poorer prognosis as compared to isolated endodontic lesions.[7,27] Healing of such defects is often marred by faster migrating epithelial tissue leading to the formation of a long junctional epithelium.[28] Primary endodontic lesions draining through gingival sulcus often get secondarily infected by plaque microorganisms that result in periodontal destruction and attachment loss. Animal and human studies have shown that reconstitution of the lost attachment apparatus can be

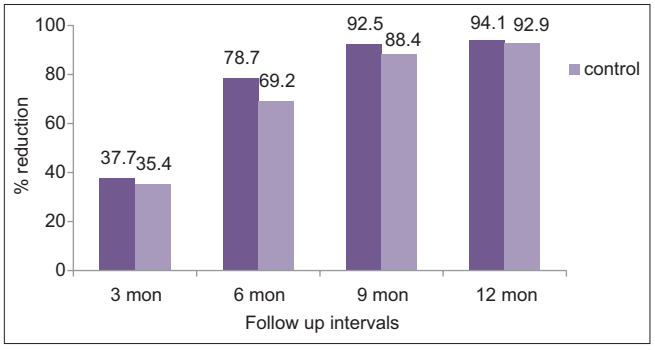
Table 1: Clinical parameters at baseline and at 12-month follow-up after surgery in the guided tissue regeneration membrane and control groups

Clinical parameters	Experimental groups	Mean±SD		*P*
		Baseline	12 months	
PD	GTR membrane group	8.91±1.67	1.16±0.38	0.002
	Control group	9.00±0.77	1.36±0.50	0.003
CAL	GTR membrane group	9.41±1.97	2.08±1.78	0.002
	Control group	9.18±1.16	2.18±1.32	0.003
GMP	GTR membrane group	−0.50±1.44	−0.91±1.78	0.059
	Control group	−0.18±0.75	−0.81±1.07	0.020

SD: Standard deviation, PD: Pocket depth, GTR: Guided tissue regeneration, CAL: Clinical attachment level, GMP: Gingival margin position



Graph 1: Reduction in the size of peri-apical radiolucencies at baseline and after 12 months post-surgical procedure.



Graph 2: Percentage reduction in the size of peri-apical radiolucencies between the groups at baseline and after 3, 6, 9 and 12 months post-surgical procedure.

Table 2: Wilcoxon signed-rank test comparing the reduction in the size of periapical radiolucencies at baseline and after 12-month postsurgical procedure

Experimental groups	Mean±SD		*Z*-cal	*Z*-tab	*P*
	Baseline	12 months			
GTR membrane group	133.58±60.94	5.00±7.39	−3.061	−1.96	0.002
Control group	166.62±177.52	19.75±32.27	−2.521	−1.96	0.012

SD: Standard deviation, GTR: Guided tissue regeneration

Table 3: Mann-Whitney test comparing the percentage reduction in the size of periapical radiolucencies between the groups at baseline and after 3, 6, 9, and 12 months' postsurgical procedure

Follow-up intervals (months)	Experimental groups (mean±SD)		U-cal	U-tab	*P*
	GTR membrane group	Control group			
3	37.76±30.19	35.43±20.76	46.000	22	0.877
6	78.76±21.40	69.25±20.80	33.000	22	0.245
9	92.50±9.52	88.42±14.32	40.000	22	0.528
12	94.13±9.87	92.90±9.08	41.500	22	0.592

SD: Standard deviation, GTR: Guided tissue regeneration

Table 4: Radiographic healing according to the criteria used by Rud *et al.* and Molven *et al.*

Radiographic healing	Complete (%)	Incomplete (%)	Uncertain (%)	Unsatisfactory (%)
GTR membrane group (*n*=12)	10 (83.33)	-	1 (8.33)	1 (8.33)
Control group (*n*=8)	7 (87.5)	1 (12.5)	-	-

GTR: Guided tissue regeneration

accomplished with regenerative techniques based on the principle of GTR.[5,6,19] It is suggested that GTR membrane barriers prevent the epithelial migration along the denuded root surfaces, thus, leading to high success rates. [15-17] However, these newer studies showing better success rates, also, incorporated modern surgical techniques and none of these tried to assess as to what extent modern techniques may have played a role in the better healing outcomes observed in the absence of GTR techniques in their studies. Kim E and Song JS, using modern microsurgical technique, reported 63.6% success rate in type E defects without any barrier technique.[23] Thus, there is a high probability that these high success rates might actually be attributed to improvements in surgical techniques and a better understanding of the biological mechanisms involved. The results of the present study suggest that isolated apico-marginal defects of endodontic origin in the anterior teeth have a tendency to heal with higher success rates with peri-apical surgery without any additional regenerative therapy.[23] The higher success rates observed in the present study as compared to Kim E and Song JS might be explained on the basis of the type of teeth treated in the study. Also, the sample, in their study, was heterogenous in nature involving anteriors, premolars and molars while the present study included only anterior teeth. Another study examining the potential prognostic factors on the outcome of endodontic surgeries involving isolated endodontic and combined endodontic-periodontal lesions found tooth position to be a pure predictor of such lesions affecting the clinical outcome.[29] In a histological study involving surgically created apico-marginal defects, Douthitt JC *et al*. observed regeneration of cementum and healthy periodontium with Sharpey's fibers in both the control and GTR membrane groups.[20] Gottlow J *et al*., in yet another histological study, observed that connective tissue attachment and bone tissue healing can, also, take place in chronic and infected apico-marginal defects created by surgically removing buccal bone.[30] Both the studies, however, reported that healing was more predictable and consistent when GTR membrane barriers were used. Significantly lower success rates observed in non-GTR membrane groups were in contradiction to the clinical observations in the present study. While GTR membrane barriers have proven to be beneficial in the management of periodontal bone losses,[18,19,31] the situation in case of isolated apico-marginal defects is different. Deep and narrow defects are more apt for regeneration as compared to wide and shallow defects. This is because configuration of apico-marginal defects is such that the narrow devoid area is surrounded favorably on all sides by healthy bone and periodontal ligament (PDL) which are a rich source of cells required for regeneration. Ingrowth of the regenerating tissue occurs not only from apical direction but, also, from the lateral aspects of the defect in such cases.[30] Such favorable circumstances may obviate the requirement of GTR membrane barriers for successful healing as was observed in the present study. Oh SL *et al*. reported successful healing of combined endodontic-periodontal lesions with grade II furcation involvement with GTR membranes.[32] They, further, reviewed articles involving successful management of combined endodontic-periodontal lesions and prepared a

treatment algorithm with an indication for GTR membranes in cases with deep and narrow defects with more than 6 mm remaining pocket depth. It is, however, significant to point-out that this treatment was suggested on the basis of the review of articles dealing with lesions belonging to different categories of Simon's classification.[33] The types of lesions included might explain the disparity in the indicated treatment plans in the studies conducted and the present study. Britain SK *et al*., also, could not observe any statistically significant differences between the healing outcomes of control and GTR membrane groups in terms of connective tissue attachment and buccal radicular bone height.[22] Regeneration of cementum, bone and periodontal ligament (PDL) on the buccal root surfaces devoid of buccal bone plate, when inter-radicular and inter-dental bone was not removed, suggests that the inter-proximal bone and healthy PDL from adjacent areas can lead to periodontal and osseous regeneration even if there is complete loss of buccal bone plate. The incidence of apico-marginal defects is relatively low. While Kim E and Song JS could find 42 defects (type E and F) out of 263 teeth in a recruitment period of 4 years,[23] Song M *et al*. could found only 27 defects out of 135 patients in a recruitment period of 7 years.[24] Similarly, Dietrich T *et al*.,[15] Marín-Botero ML *et al*.[16] and Goyal B *et al*.[17] could find only 24, 30 and 25 apico-marginal defects respectively in their studies.

Limitations of the present study

The major limitations of the present study included:

1. Clinical and radiographic evidence of newly formed bone does not necessarily indicate regeneration, hence, histological evaluation is ideally needed to confirm the efficacy of collagen membrane in promoting regeneration of peri-apical and periodontal tissues;
2. Heterogeneous nature of apico-marginal defects (each individual defect differs in shape and pattern of bone loss) and difference in the amount of remaining periodontal support may, also, influence regeneration;
3. Small number of sample size with variability in the type of defects might lack statistical power; while
4. Drop-outs during follow-up of the patients was another limitation noted during the present study.

Conclusion

Due to low incidence of apico-marginal defects, the present study could enroll only 30 patients in a recruitment period of 12 months out of which 7 patients were lost during follow-up. Although the study reported no statistical difference between the success rates with or, without GTR membrane in the treatment of apico-marginal defects, further well-controlled, long term clinical trials with larger sample sizes are required to confirm the outcome of the regenerative therapy in such defects. Further, the exact composition of the repaired area could not be commented upon as this was not a histological study. Within the limitations of the present study, the results indicated that there might not be any additional clinical advantage obtained from GTR membrane barriers in the surgical management of isolated apico-marginal defects of primary endodontic origin with absent or, minimal inter-proximal bone loss.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Hirsch JM, Ahlström U, Henrikson PA, Heyden G, Peterson LE. Peri-apical surgery. Int J Oral Surg 1979;8:173-85.
2. Skoglund A, Persson G. A follow-up study of apicoectomized teeth with total loss of the buccal bone plate. Oral Surg Oral Med and Oral Pathol 1985;59:78-81.
3. Rankow HJ, Krasner PR. Endodontic applications of guided tissue regeneration in endodontic surgery. J Endod 1996;22:34-43.
4. Mikkonen M, Kullaa-Mikkonen A, Kotilainen R. Clinical and radiologic reexamination of apicoectomized teeth. Oral Surg Oral Med Oral Pathol 1983;55:302-6.
5. Dahlin C, Linde A, Gottlow J, Nyman S. Healing of bone defects by guided tissue regeneration. Plast Reconstr Surg 1988;81:672-6.
6. Nyman S. Bone regeneration using the principle of guided tissue regeneration. J Clin Periodontol 1991;18:494-8.
7. Abramowitz PN, Rankow H, Trope M. Multidisciplinary approach to apical surgery in conjunction with the loss of buccal cortical plate. Oral Surg Oral Med Oral Pathol 1994;77:502-6.
8. Kellert M, Chalfin H, Solomon C. Guided tissue regeneration: An adjunct to endodontic surgery. J Am Dent Assoc 1994;125:1229-33.
9. Tseng CC, Harn WM, Chen YH, Huang CC, Yuan K, Huang PH. A new approach to the treatment of true-combined endodontic-periodontic lesions by the guided tissue regeneration technique. J Endod 1996;22:693-6.
10. Brugnami F, Mellonig JT. Treatment of a large peri-apical lesion with loss of labial cortical plate using GTR: A case report. Int J Periodontics Restorative Dent 1999;19:243-9.
11. Uchin RA. Use of bio-resorbable guided tissue membrane as an adjunct to bony regeneration in cases requiring endodontic surgical intervention. J Endod 1996;22:94-6.
12. Milano F, Melsen B. Guided tissue regeneration using bio-resorbable membranes: What is the limit in the treatment of combined peri-apical and marginal lesions? Int J Periodontics Restorative Dent 1997;17:416-25.
13. Blank BS, Levy AR. Combined treatment of a large periodontal defect using GTR and DFDBA. Int J Periodontics Restorative Dent 1999;19:481-7.
14. Pompa DG. Guided tissue repair of complete buccal dehiscence associated with peri-apical defects: A clinical retrospective study. J Am Dent Assoc 1997;12:989-97.
15. Dietrich T, Zunker P, Dietrich D, Bernimoulin JP. Peri-apical and periodontal healing after osseous grafting and guided tissue regeneration treatment of apico-marginal defects in peri-radicular surgery: Results after 12 months. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;95:474-82.
16. Marín-Botero ML, Domínguez-Mejía JS, Arismendi-Echavarría JA, Mesa-Jaramillo AL, Flórez-Moreno GA, Tobón-Arroyave SI. Healing response of apico-marginal defects to two guided tissue regeneration techniques in peri-radicular surgery: A double-blind, randomized-clinical trial. Int Endod J 2006;39:368-77.
17. Goyal B, Tewari S, Duhan J, Sehgal PK. Comparative evaluation of platelet-rich plasma and guided tissue regeneration membrane in the healing of apico-marginal defects: A clinical study. J Endod 2011;37:773-80.
18. Nyman S, Lindhe J, Karring T, Rylander H. New attachment following surgical treatment of human periodontal disease. J Clin Periodontol 1982;9:290-6.
19. Gottlow J, Nyman S, Lindhe J, Karring T, Wennström J. New attachment

formation in the human periodontium by guided tissue regeneration: Case reports. J Clin Periodontol 1986;13:604-16.
20. Douthitt JC, Gutmann JL, Witherspoon DE. Histologic assessment of healing after the use of a bio-resorbable membrane in the management of buccal bone loss concomitant with peri-radicular surgery. J Endod 2001;27:404-10.
21. von Arx T, Britain S, Cochran DL, Schenk RK, Nummikoski P, Buser D. Healing of peri-apical lesions with complete loss of the buccal bone plate: A histologic study in the canine mandible. Int J Periodontics Restorative Dent 2003;23:157-67.
22. Britain SK, Arx Tv, Schenk RK, Buser D, Nummikoski P, Cochran DL. The use of guided tissue regeneration principles in endodontic surgery for induced chronic periodontic-endodontic lesions: A clinical, radiographic, and histologic evaluation. J Periodontol 2005;76:450-60.
23. Kim E, Song JS. Prospective clinical study evaluating endodontic microsurgery outcomes for cases with lesions of endodontic origin compared with cases with lesions of combined periodontal- endodontic origin. J Endod 2008;34:546-51.
24. Song M, Kim SG, Shin SJ, Kim HC, Kim E. The influence of bone tissue deficiency on the outcome of endodontic microsurgery: A prospective study. J Endod 2013;39:1341-5.
25. Rud J, Andreasen JO, Moller-Jensen JE. Radiographic criteria for the assessment of healing after endodontic surgery. Int J Oral Surg 1972;1:195-214.
26. Molven O, Halse A, Grung B. Observer strategy and the radiographic classification of healing after endodontic surgery. Int J Oral Maxillofac Surg 1987;16:432-9.
27. Jansson L, Sandstedt P, Laftman AC, Skoglund A. Relationship between apical and marginal healing in peri-radicular surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;83:596-601.
28. Melcher A. On the repair potential of periodontal tissues. J Periodontal 1976;47:256-60.
29. Song M, Jung IY, Lee SJ, Lee CY, Kim E. Prognostic factors for clinical outcomes in endodontic microsurgery: A retrospective study. J Endod 2011;37:927-33.
30. Gottlow J, Nyman S, Karring T, Lindhe J. New attachment formation as the result of controlled tissue regeneration. J Clin Periodontol 1984;11:494-503.
31. Nyman S, Gottlow J, Lindhe J, Karring T, Wennstrom J. New attachment formation by guided tissue regeneration. J Periodontal Res 1987;22:252-4.
32. Oh SL, Fouad AF, Park SH. Treatment strategy for guided tissue regeneration in combined endodontic-periodontic lesions: Case report and review. J Endod 2009;35:1331-6.
33. Simon JH, Glick DH, Frank AL. The relationship of endodontic-periodontic lesions. J Periodontol 1972;43:202-8.