Evaluation Of Collegen Membrane Placement With Bone Graft In Tooth Socket Preservation: An Original Research

[1]Dr. Rajeev Pathak, [2]Dr. Varun Salgotra, [3]Dr. A Rashmi Pillai, [4]Dr. Nivya John, [5]Dr. Shilpa Duseja, [6]Dr. Mayank Sharma

[1]Professor, Department of Periodontology, Teerthanker Mahaveer Dental College and Research center, Moradabad, U.P, India
[2]Reader, Department of Oral and Maxillofacial Surgery, Pacific Dental College and Research Centre, Rajasthan, India
[3]MDS, Oral and Maxillofacial Surgeon, Rashmis Dentofacial Multispeciality Centre, Kavanad, Kollam, Kerala, India
[4]Lecturer, Department of Prosthodontics and Oral Implantology, AB Shetty Memorial institute of Dental Sciences, Nitte deemed to be University, India
[5]Professor, Department of Periodontology, Narsinhbhai Patel Dental College and Hospital, Sankalchand Patel University, Visnagar, India
[6]Senior Dentist, Central Coast Dental Care, Seaside, CA

Corresponding Author: Dr Rajeev Pathak,
dr.rajeev73@gmail.com

ABSTRACT

Aim: The primary objective of the randomised research study is to evaluate and compare the efficacy of collagen membrane alone and the combination of collagen membrane with porcine-derived bone grafts in tooth socket preservation.

Introduction: Tooth socket preservation is an important step to completing the entire dental implant surgery successfully. Generally, most dentists prefer to use bone graft materials and collagen membranes after tooth extraction. In the current scenario, the use of the resorbable collagen membrane is gaining popularity compared to other materials. Collagen membranes possess many imperative biophysiological qualities, which include being biocompatible, less inflammatory, less time-consuming, biodegradable, requiring no additional surgery, and being more patient-friendly than non-resorbable membranes. They play a key role in the regeneration of osseous defects in periodontal pockets.

Materials and Methods: 30 healthy patients without any history of critical bone wall defects in the molar or premolar regions, and having single extraction sockets were included. The studies were divided into three groups. Ten extraction sockets were grafted with bone obtained from porcine and enclosed with collagen membrane (group 1), ten sites were enclosed with only collagen membrane (group 2), and another 10 sites were kept for self-healing (group 3). After a period of four months postoperatively, 26 bone core samples (8 in group 1, 9 in group 2, and 9 in group 3) were taken for histologic assessment, and after that, dental implants were inserted.

Results: Corresponding histologic and histomorphometric results were found in the socket sites of groups 1 and 2 without notable differences in the percentage of healed or newly formed bone (57.43% [SD 4.8] vs. 60.01% [SD 3.2]) and non-ossified connective tissue 22.99% (SD 5.3) vs. 18.53% (SD 6.2). In group 1a, 16.57 (SD 3.8) residual elements were obtained.

Conclusion: A notable and measurable clinical outcome was observed in both the alone and combined use of collagen membrane and porcine-derived bone graft as compared to the spontaneous healing of extraction sites. Moreover, histomorphometric data, which shows bone strength, illustrated that there is no requirement of more than 4 months for dental

implant placement; the thickness of extraction sites without critical wall fault and with a vestibular bone was > 1.5 mm, subjected to low resorption rate collagen membrane alone.
Key words: periodontal, collagen membrane, bone graft, histomorphometric, ossified.
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INTRODUCTION

Tooth sockets are a space in the jaws where the roots of teeth remain attached in the alveolar process (the massive ridge of the bone has tooth sockets to hold teeth in the mandible and maxilla). [1] The word periodontium refers to all the surrounding tissues that tie up teeth in the maxillary and mandible. The periodontium comprises four integral parts: gingiva, cementum, periodontal ligament (PDL), and alveolar bone. [2] The principal reason behind bone loss is periodontitis, which causes menacing gum ulceration due to injury and destruction of the network of periodontal-bone ligament bundles, damaged teeth, endodontic inflammation, etc. [3] Alveolar bone recedes hastily after tooth extraction as a result of physiological and functional changes in alveolar bone, leading to shrinkage and loss of surrounding bone and gum density. This leaves an unpleasant facial look by manifesting lips and cheek slumps, which also challenge dental prostheses such as crowns, dentures, dental implants, bridges, veneers, etc. [4] After traumatic tooth extraction, the aim of every dental surgeon is to maintain or reduce alveolar bone recession and constricting of gums, soft tissues, and hard tissue in view of the fact that lost alveolar ridge dimension is an irreversible action. To minimise and control this loss, alveolar ridge preservation techniques have been developed to regenerate and replace bone tissue post-tooth extraction, especially during orthognathic surgery. [5] Any morphological and functional changes in the alveolar socket might be determined by the alteration of width, height, size, metabolic factors, and mucosal thickness. The resorption process was observed to be speedy in the first 3 to 6 months. As reported by the current systematic review evaluation, the variation of the vertical and horizontal bone loss in the alveolar ridge has been found to be 11% to 22% and 29% to 63%, respectively, during the period of 6 months, then gradually decreases, followed by buccal bone resorption, which has been found up to 56%, whereas hyoid bone has been noticed to have less resorption than buccal bone. It is very important to have intact alveolar bone and tissues around it to successfully implant new teeth and maintain facial aesthetics. [6] To facilitate dental implants post extraction, there are generally two types of methods to protect the alveolar bone socket: (1) guided bone regeneration (GBR) and (2) guided tissue regeneration (GTR). The aim of guided bone regeneration is to place a tissue-occlusive membrane barricade between the epithelium, connective tissue, and alveolar ridge defected area, with or without bone substitutes and bone graft materials. The principal objective of the membrane barrier is to prevent cells that hinder growth (e.g., gingival fibroblasts, epithelial cells). Bone regeneration occurs via the emigration of pluripotent osteogenic cells that originate from the bone marrow and periosteum towards disrupted alveolar bone cells. After GBR application, the following sequence happens: after 24 hours of a bone graft, the place made by the barrier/graft material becomes full of thrombus, leading to the activation of various growth factors (IL-8, PDGFR-α and –β) results in the invitation of macrophages and neutrophils. The clot disappears gradually, leading to the augmentation of fresh connective tissues and blood vessels. Via these blood vessel, nutrients and multipotent cells can be easily diffused to the target site and promote osseous differentiation. [7, 8] the objective of GTR is to reconstruct and reproduce a collapsed and bruised area in such a way that the structure and function of collapsed and bruised tissues are completely recovered. The GTR is based on Melcher's hypothesis that only four types of connective tissues are able to repopulate the root surface during periodontal surgery, i.e., (1) lamina propria of gingiva, (2) PDL, (3) cementum, and (4) alveolar bone. The main function of GTR is to prevent migration of epithelium by keeping

the membrane between the flap and tooth socket (hindering contact of the connective tissue with the root surface); cells isolated from the periodontal membrane are prompt on the root surface, specifically leading to regeneration and restoration of periodontal tissue. [9] biological modes of action of bone grafts have been derived from three types of mechanisms: osteoinduction, osteoconduction, and osteogenesis.[10, 11]

COLLAGEN MEMBRANE

Now a day, use of collagen membrane placement with bone graft in tooth socket preservation has gained momentum in both GTR and GBR to support the graft materials, control their resorption, and act as an occlusive barrier to limit fibrous tissue infiltration and promote bone regeneration in the surrounding area. The collagen membrane has been found to be extremely biocompatible, without any inflammatory cells observed at the site of surgery. The collagen membrane degenerates completely between 4-6 months; during this time, both bone and soft tissue get well incorporated. [12] Collagen is a protein moiety made up of amino acids. Its unique physiological structure, and stiffness and stretch opposing functions provide excellent support to the intercellular matrix of connective tissues. There are approximately 28 types of collagen that have been seen so far in the bone matrix, ligaments, tendons, cartilage, vitreous of the eye, blood vessels, basement membrane, epithelial, etc.; 80-90% of the body's collagen is made up of types 1, 2, and 3. The collagen possesses amazing biological qualities: due to its biocompatibility and healing properties, used in dentistry, it has weak immunogenicity, homeostasis, the ability to captivate and stimulate periodontal ligament and gingival fibroblast cells, and tissue growth, while the process of wound healing interaction with other cells takes place.Various scientific studies have found collagen membrane has better wound healing and bone regeneration properties than synthetic non- resorbable materials. Collagen membranes are isolated from many porcine and bovine tissues (e.g., tendon, small intestine, skin, etc.), and their absorption and degradation rate depend on the source of animals. But there are some disadvantages, such as their low rigidity, which makes them more applicable to the types of alveolar bone damage that do not require additional strength and built such as fenestration and bone dehiscence. Data also shows that sometimes it degrades before proper bone regeneration, to overcome such conditions and transform less stable collagen membrane into stronger ones. Number of modifications generally treated with aldehyde via covalent bond, leading to decreased water absorption, solubility, and increasing stretching power, FDA approved collagen for human use. Collagen membrane resorption is initiated by the matrix metalloproteinase, which breaks the collagen membrane into small pieces, which then transform into gelatin, which is further degraded to amino acids through gelatinase and other proteinases. In between, it connects with the flap to encourage new connective tissue encroachment, resulting in tissue thickness and bone regeneration. [13, 14]

MATERIAL AND METHODS

Thirty patients were enrolled in the research for a period of three months who were suffering from periodontal defects, requiring the extraction of a single molar or premolar tooth, and willing to undergo dental implant treatment. Extraction sites that have to be fixed were subjected to cover with a porcine-derived resorbable collagen membrane alone, considering the 12-14 week resorption time (Mem-Lok Pliable, BioHorizons, Birmingham, AI, USA), or a combination of resorbable collagen membrane derived from porcine and bone graft material (obtained from porcine-based bone mineral matrix, particle size between 250 and 1000 mm (MinerOss XP, BioHorizons, Birmingham, AI, USA).

The following criteria were required for the study:

- Age ≥18 years;
- Healthy volunteers, no pregnancy, free from any metabolic disorders;

- Sufficient space for filling and implant-retained restoration;
- Approximately 10 mm of alveolar bone height and a healthy maxillary sinus or mandibular canal, confirmed by intraoral radiographies or cone beam computed tomography (CBCT) scans.

The exclusion criteria were:

- Diseases that hamper dental surgery;
- History of non-steroidal anti-inflammatory drug therapy;
- Pregnancy or lactating mother;
- Oral bisphosphonate therapy;
- Uninterested in regular follow-up assessments;
- Cigarette smoking > 10 per day;

Absence of more than half of the lingual/vestibular socket wall, checked before surgery by intraoral radiographies and CBCT scans or throughout the extraction of the tooth using a graded periodontal probe (CP 15 UNC, HU-Friedy, Chicago, USA).

Division of patients into three groups of 10 patients each:

Group 1: combination of extracted sockets grafted with porcine-derived bone and sheaths with collagen membrane;

Group 2: sockets covered only with collagen membrane;

Group 3: Extracted sockets with self-healing;

The patients were randomly allocated to groups 1, 2, and 3 by a computer-generated random number table. All data was stored on portable computers and protected by a password. Encased in serially numbered, identical, esoteric, sealed envelopes, only persons who perform research were allowed a third person not involved in enrolment or data collection. Approval had been obtained from the Ethical Committee of University (Ref No. 4597).

HISTOLOGIC ANALYSIS

Bone specimens (8 mm in length) were taken during the insertion of implants after 4 months of grafting operations, using a trephine drill with a 2.5 mm internal diameter. Treated and fixed with a 10% buffer solution of formalin and ingrained in a glycolmethacrylate resin, specimens were sectioned longitudinally to a thickness of 70 microns (Plastic Microtome, RM 2265). Slides were stained with Trichromic and Methylene Blue/Basic Fuschin, and postpolymerization assessment was done using an Olympus B51 microscope (Olympus America, Lake Success, NY, USA). The interior area of each section (0.1 mm^2) was selected for histomorphometric analysis, and the area fraction percentage of each element in each section was measured automatically via Bioquant®, an image analysis software (R&M Biometrics Nashville, TN, USA), and images were captured by a Q-Imaging camera, 32-0013B-157, RETIGA, colour 12-bit. After approval by the American Society of Bone and Mineral Research, bone quality and histomorphometric measurements were recorded and analysed by a blinded researcher via Ky Plot 2.0 software, Informer Technologies, Inc., NY, USA.

STATISTICAL ANALYSIS

For each parameter, the standard deviation and mean value were calculated and compared via a nonparametric Mann-Whitney U test for unpaired data. $P < 0.05$ level of significance had been taken for all statistical comparisons performed.

Table 1 Dependent variables and demographic data obtained for the three experimental groups

Dependent variables and demogeaphies	Group 1	Group 2	Group 3
Patients (n)	8	9	9
Age (years)	20-63	19-60	21-56
Sex (male/female)	6/2	3/6	5/4
Premolar/molar	4/4	6/3	4/5
Smoking habit (yes/no)	3/5	3/6	2/7

n = number; Group 1 = Combination of collagen membrane and graft material obtained from porcine; Group 2 = Collagen membrane derived from porcine alone; Group 3 = Self-healing

RESULT

4 patients were excluded due to greater vestibular dehiscence, that is, more than 50% of the vestibular socket wall was found amidst periodontal extractive surgery using a periodontal graded probe, so 26 patients (14 males and 12 females with an average age of 46.7, ranging between 20-63 years) were included and divided into the study groups. 8 patients were in the group 1, and 8 and 9 patients were included in the corresponding groups 2 and 3. At the final steps of the study, 26 bone samples were taken and 26 dental implants (Laser-Lok Tapered, BioHorizons, Birmingham, AI, USA) were placed. Dependent and demographic variables for each group are analysed and recorded in Table 1.

Normal, healthy trabecular bone structures were observed in groups 1 and 2 via morphological analysis. The highest number of osteoid cells at different stages of mineralization was observed in Group 1. Connective tissues and osteoid matrices were found to be restricted in number, with mature trabecular organisations in Group 2. Group 3 showed an enormous amount of woven bone as well as connective tissues and narrow trabecular organisations.

Table 2 represents the histomorphometric comparative findings of the three research groups. Whereas histomorphometrically, in the self-healed sockets, the percentage of vital bone was 48.85 (2.3), and the percentage of connective tissues was observed at 34.17% (4.1). On the other hand, the extracted sites treated with only collagen membrane show percentages of osteogenesis and connective tissues, respectively, of 60.01 (3.2) and 18.53 (6.2), while osteogenesis and non-mineralized connective tissue in the combination of collagen membrane and porcine xenograft were found at 57.43 (4.8)%, and 22.99 (5.3)% respectively. A statistically significant ($P > 0.05$) value was found for the difference between self-healed sockets and treated sockets, whereas the difference between the combination of collagen membrane and xenograft and membrane alone was non-statistically significant. The percentage of left-over graft material treated with membrane and xenogenic bone was reported at 16.57 (3.8). The data shows that, collagen membrane with bone graft materials showed a higher percentage of osteoid tissue/area compared to self-healed sockets and sockets treated with membrane alone.

Table 2 Histomorphometric analysis

	Group 1 Mean (SD)	Group 2 Mean (SD)	Group 3 Mean (SD)	Significance, P < 0.05
Tt. tissue area ($mm^{2)}$	14.23 (3.3)	11.39 (2.9)	12.28 (2.1)	-
Tt. area of bone (mm^2)	6.708(0.3)	7.061(0.5)	6.942(0.7)	-
Tt. area of bone graft (mm^2)	2.506(0.6)	0	0	-
% **connective tissue/Tt. area**	22.99(5.3)	18.53(6.2)	34.17(4.1)	3 vs 2/1

% **bone/Tt. tissue area**	57.43(4.8)	60.01(3.2)	48.85(2.37)	3 vs 2/1
% **graft/Tt. tissue area**	16.57(3.8)	0	0	-
Tt. osteoid area (mm^2)	0.568(0.4)	0.312(0.2)	0.284(0.4)	3/2 vs 1
Tt. connective tissue area (mm^2)	0.703(0.1)	0.871(0.4)	3.943(0.2)	3 vs 2/1
Tt. bone marrow area (mm^2)	2.048(0.2)	2.265(0.2)	2.134(0.3)	-
Tt. bone surface	92.9(9.8)	82.95(8.3)	89.76(9.7)	-
Tt. osteoid surface	25.94(3.6)	11.71(2.4)	9.58(1.7)	3/2 vs 1
% **osteoid/Tt. bone surface**	21.62(2.9)	12.06(2.7)	10.23(2.1)	3 vs 2/1
Trabecular thickness	170.3(14.5)	181.8(15.9)	142.4(11.4)	3 vs 2/1
Trabecular number	3.64(1.1)	4.21(1.4)	3.89(0.6)	-
Trabecular space	125.5(12.5)	124.3(11.9)	112.7(14.8)	3 vs 2/1
% **inflammatory cells/Tt. tissue area**	1	1	1	-

SD = standard deviation; Tt. = total biopsy core. Group 1, treated with graft and membrane; Group 2, treated with membrane alone; Group 3, spontaneously healed.[15]

DISCUSSION

The outcome of the following results compliments previously published research. [15] Study showed that the application of resorbable collagen membrane alone and the combination of collagen membrane and porcine-derived bone graft materials had better bone healing compared to that of extraction sites that self-healed. These results also supported the data found from the other research studies and justified that the bone graft material obtained from porcine and resorbable membrane is fruitful in restoring the post-extractive alveolar ridge volume compared to self-healed extraction sites.[16, 17] As former data, the comparative clinical studies of three experimental groups and reassessment at the time period of 4 months found that extraction sockets grafted with porcine-derived bone and/or covered by collagen membrane represent notable lower horizontal and vertical bone changes when the extraction sockets are free from any critical wall deficiency and with vestibular bone thickness ≥ 1.5 mm, compared to extraction sockets left for self-healing.[15] Furthermore, based on Juodzbalys et al.'s classification.[18] In type 1 premolar extraction sockets with vestibular bone thickness ≥ 1.5 mm, both the use of collagen membrane alone and membrane with bone graft materials showed similar clinical results. Histological and histomorphometric clinical data represent and justify that when extraction sockets are free from any critical wall deficiency and vestibular bone thickness ≥ 1.5 mm, collagen membrane with a low rate of resorption (12-14 weeks) can be used alone in socket preservation. The examination of core bone specimens taken from the extraction sites found a total tissue/bone area of 60.01%, a mean trabecular thickness of 181.8 (15.9) µm, and a mean trabecular number of 4.21 (1.4) mm^{-1}. This finding could be correlated to the physiochemical properties of the collagen membrane used in the *in vitro* study, which include a low inflammatory and immunogenic response, while the same collagen membrane showed a notably higher average suture pull-out strength and higher stability than conventional collagen membrane.[19] It is also hypothesised that the higher stability and low resorption (12/14 weeks) rate are responsible for making the membrane have adequate space and firmness, which leads to less involvement of foreign bodies and inflammatory reactions, which results in increased tissue integration and wound healing. Group that is self-healed found a lesser 48.85% of bone/total tissue area, a mean trabecular thickness of 142.4 (11.4) mm, and a mean trabecular number of 3.89 (0.6) for mm^{-1} with an

increased quantity of woven bone, connective tissue, and osteoid matrix. There might be an argument that it is unnecessary to wait over 4 months post-extraction of teeth and prior to dental implant placement when the collagen membrane with the lowest resorption rate was chosen compared to collagen membrane alone and the combination of both collagen membrane and porcine-derived graft materials showed a similar percentage of regeneration of bone, a mean trabecular thickness, and a mean trabecular number at 4 months of re-entry surgery; moreover, the quantity of 16:57 (3:8)% of residual graft materials regardless of the presence of residual graft particles, as compared to sites without residual graft materials, this site did not receive any sense of touch from drilling into better quality bone or poorer-quality bone during the implant insertion or surgery after the 4 months of extraction. The failure of immunogenic stimulation and absence of inflammatory response observed in porcine-derived bone graft materials indicate that the biomaterial function as an osteoconductive materials. Therefore, the tremendous amount of osteoid tissues that surround residual graft materials and the simultaneous continuation of absorption process and regeneration of bone around residual graft materials indicate indirectly that they delay the healing process. The purpose of the bone grafting is to achieve 100% regenerative bone and supportive tissues that sustain the remodelling process. The ideal graft material should be able to minimise ridge remodelling but also fasten bone formation to shorten the treatment time. The level of resorption of graft materials depends on several factors; including pore size, morphology, and percentage, inter connection between pores, granulometry.[20-25] this leads to better infiltration of nutrients and oxygen, and a greater number of osteoblasts, which also promotes angiogenesis. Moreover, it also depicts better interconnection between the osteoblast cells and the graft particles. The average pore size of porcine-derived bone matrix used in the study is 474.26 (76.2) µm with a trabecular thickness of 121.76 (21.9) µm, and a pore connectivity of 88 – 95%, which are similar to those of human bone.[26] This quality represents a high resorption rate (83.43%) of porcine-derived graft materials, but until now, controversy has remained over whether the porcine-derived bone is completely resorbable.[27] The occurrence of non-resorption is to protect newly formed bone from physiological stress, which is crucial for bone regeneration, but it might be possible that the presence of residual graft materials interferes with the osteogenesis of dental implants and the inter-connectivity between bone and implant.[28,29] However, according to other authors, the granule population around the dental implants could depict the locus *minoris resistentiae* in cases of peri-implant infections.[30] Moreover, the absolute intimacy of the residual bone graft with the bone led to a stiff and compact tissue matrix that surrounds the vital bone. Some authors also suggest that once the residual graft particles were completely intermixed in the bone, they acted with similar biological functions as the host bone.[17, 18] some authors believe that the presence of residual bone graft materials has a negative impact and hampers the healing process.[31, 32]

CONCLUSION

The histologic and histomorphometric findings of the present research conclude that the use of collagen membrane alone and a combination of porcine-derived graft materials boost the bone healing process as compared to self-healing. The study also found that there is no notable difference when applying collagen membrane alone or with porcine-derived bone graft in the percentage of vital bone, mean trabecular thickness, number, and extraction sockets free from any damages in the wall, and with a vestibular wall thickness (P > 1.5 mm). Although osteoid tissue is abundantly found around the residual graft materials, which depict bone, it continues maturing. However, histomorphometric reports showed it is unnecessary to wait over 4 months for dental implant placement when socket sites are free from alveolar wall defects and wall bone thickness > 1.5 mm and treated with collagen membrane alone.

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