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ORIGINAL ARTICLE

Evaluation of hyaluronic acid gel with or without acellular dermal matrix allograft in the treatment of class II furcation defects in dogs: A histologic and histomorphometric study

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Biomaterials;
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Wound healing

Abstract *Aim:* To evaluate the histologic and histomorphometric effects of hyaluronic acid (HA) gel with or without acellular dermal matrix allograft (ADMA) on periodontal regeneration in Class II furcation defects in dogs.

Materials and methods: Class II furcation defects were surgically created in the mandibular first and second premolars bilaterally in eight beagle dogs. The Class II furcation defects were assigned randomly, using the split-mouth design, into the test and control sides. The teeth on the test sides were equally and randomly divided into the HA/ADMA group (n = 8) treated with 0.8% HA gel followed by ADMA, and the HA-only group (n = 8) treated with 0.8% HA only. The furcation defects of the control sides (n = 16) were subjected to open flap debridement (OFD group). The animals were euthanized for histologic and histomorphometric analyses after one month (n = 4) and three months (n = 4).

Results: At one month, the newly formed bone area (NFBA) was larger in the HA/ADMA (6.23 ± 1.41 mm^2) and HA-only (5.90 ± 1.43 mm^2) groups than in the OFD group (2.42 ± 1.62 mm^2) ($p < 0.05$). The newly formed cementum (NFAC) and periodontal ligament (NFPL) were similar in the HA/ADMA and HA-only groups but significantly lesser in the OFD group ($p < 0.05$.) At three months, the NFBA, NFAC, and NFPL were greater in the HA/ADMA group than in the HA-only group ($p < 0.05$). New regenerative tissue was significantly greater in both the

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test groups than in the OFD group ($p < 0.05$), while epithelial downgrowth predominated the healing in the latter.

Conclusions: These results suggest that HA with ADMA positively affects the periodontal regeneration and wound healing in Class II furcation defects.

1. Introduction

The treatment of furcation defects is a challenging aspect of periodontal therapy. Anatomical factors in the furcation area limit the accessibility for instrumentation and lead to a compromised response to the conventional periodontal treatments (Nibali et al., 2016, Gill et al., 2022). Therefore, molars with furcation defects are considered to have worse prognosis than those without (Nibali et al., 2016). Although several studies have investigated regenerative periodontal therapy in treating furcation defects, their results have been inconsistent (Avila-Ortiz et al., 2015, Sanz et al., 2015, Jepsen et al., 2020, Rasperini et al., 2020).

Biomaterials, such as barrier membranes, bone substitutes, and biologics/growth factors, have been used in periodontal regenerative procedures in a single or combination approach. However, there are no guidelines regarding the use of materials or techniques for successful outcomes. Evidence suggests the use of a combination approach, and adding biological mediators provides the best outcomes in the treatment of Class II defects (Reddy et al., 2015, Laugisch et al., 2019).

Hyaluronic acid (HA) is a naturally occurring high molecular weight polysaccharide showing promising results in periodontal regeneration (Bansal et al., 2010). HA is essential for maintaining the structural and homeostatic integrity of tissues. It positively affects cell migration, proliferation, and angiogenesis thereby promoting periodontal wound healing (Dahiya and Kamal 2013). When used as part of non-surgical periodontal therapy, a marked reduction in the probing pocket depth and gain in the clinical attachment level was documented (Polepalle et al., 2015, Shah et al., 2016).

Acellular dermal matrix allograft (ADMA) has been used as an alternative to autogenous soft tissue grafts in different mucogingival procedures with reliable and predictable results (Novaes and Palioto 2019). It has been used in root coverage procedures (Yaghini et al., 2023), treatment of ridge deformities (Yaghini et al., 2023), keratinized tissue augmentation around teeth and implants (Panwar et al., 2022), gingival phenotype modification (Barootchi et al., 2020), and as a barrier membrane in guided bone regeneration (GBR) (Sudarsan et al., 2008, Borges et al., 2009).

The data on the effects of HA alone or in combination with ADMA on Class II furcation regeneration is scarce. Therefore, this study aimed to assess the impact of HA with or without ADMA on periodontal regeneration in Class II furcation defects in dogs.

2. Materials and methods

The study protocol was approved by the Scientific Research Ethics Committee at the Faculty of Dentistry, Alexandria University (Approval number: IORG0008839).

2.1. Animal preparation

We included eight adult male mongrel dogs weighing 10–15 kg. Dogs were kept at an animal healthcare facility (Faculty of Medicine, Department of Physiology, Alexandria University, Egypt) with unrestricted access to water and food. Oral prophylaxis and topical 0.12% chlorhexidine were used for plaque control.

2.2. Surgical protocol

Full-thickness flaps surgeries were performed to create buccal Class II furcation defects in mandibular first and second premolars (P1 and P2) bilaterally. A standard defect measuring 5 mm in height, measured using a periodontal probe from the furcation fornix to the base of the defect, and 3 mm in depth, measured from the buccal surface, was created (Fig. 1).

To prevent the occurrence of spontaneous repair, a rubber-base impression material was placed in the furcation area (Selvig 1994). The flaps were repositioned and sutured using a non-absorbable suture. All animals were fed a soft diet for two weeks to allow plaque accumulation and gingival inflammation. Then, the impression material was removed, and the roots were scaled thoroughly. Plaque control was maintained by daily topical application of 0.12% chlorhexidine in the subsequent weeks.

2.3. Regenerative surgery

Two weeks after removing the impression material, regenerative surgeries were performed. A full-thickness flap was elevated, the granulation tissue was removed, and the exposed root surfaces were scaled and planed. Reference notches were made in the mesial and distal roots, using a small round bur, at the base of the defect as a guideline for histologic and histomorphometric analyses.

The furcation defects were randomly assigned to the test and control sides using the split-mouth design. The furcation defects of one group of teeth on the test sides ($n = 8$) were treated with 0.8% HA gel (Gengigel® Ricerfarma, Milano, Italy) and covered by ADMA (AlloDerm, LifeCell Corporation, Woodlands, TX, USA) (HA/ADMA group). The ADMA was trimmed to cover the furcation and extended to the adjacent bone by 3 mm apically and laterally. It was positioned slightly coronal to the cementoenamel junction and sutured using bioabsorbable sutures (Fig. 1D). The furcation defects of the other test group ($n = 8$) were treated with 0.8% HA gel (HA-only group). Finally, the flaps were repositioned coronally and sutured to cover the defect completely (Fig. 1E). The furcation defects of the teeth on the control side ($n = 16$) were subjected to open flap debridement (OFD group).

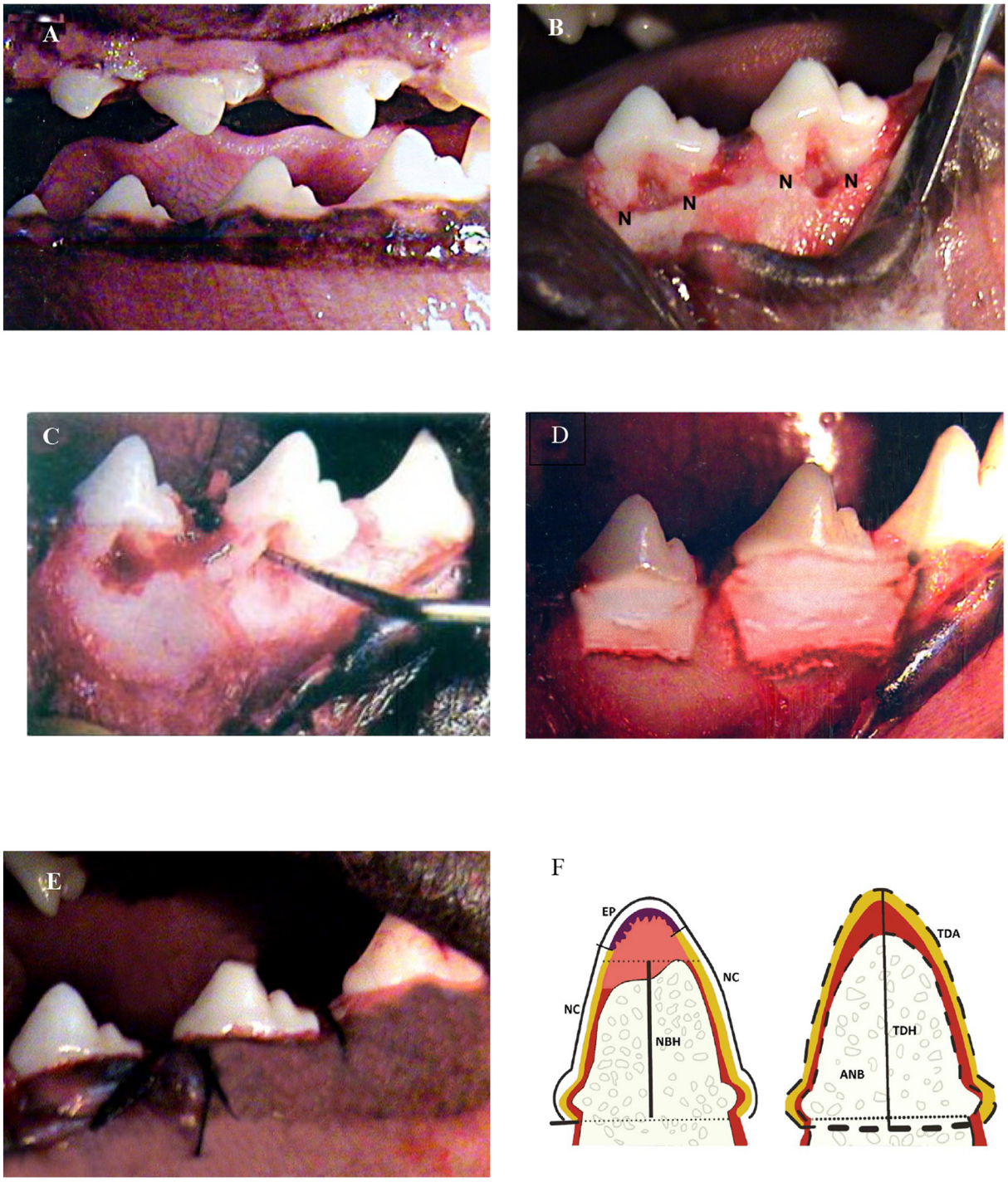

Fig. 1 **A:** Mandibular left first and second premolars (P1 and P2) before surgery. **B:** Creation of class II furcation buccal defects with notches (N) at P1 and P2 roots. **C**: Periodontal prob confirm the horizontal defect depth (3 mm). **D**: ADMA membrane with HA covering the furcation defects. **E**: Interrupted suture with complete coverage of the ADMA in group I. **F:** Schematic representation of area and linear measurements evaluated in histometric analysis [Total defect area (TDA), Total defect height (TDH), Area of new bone (ANB), Epithelial down growth (EP), New cementum (NC), New bone height (NBH)]. (Selvig 1994).

2.4. Postsurgical care

The animals received Acupan intramuscularly every 12 h for pain control and tetracycline hydrochloride 125 mg IM for the first two days (Shirakata et al., 2022). The antibiotic was mixed in the dogs' food for seven days.

2.5. Histological evaluation

The dogs were euthanized at one month (n = 4) and three months (n = 4) postoperatively for histological evaluation. The furcation defect tissues with the surrounding bone were dissected and the specimens were embedded in paraffin blocks.

All formalin-fixed-paraffin-embedded tissues were serially cut in mesiodistal sections of 5 μm thickness and stained with hematoxylin & eosin stain.

2.6. Histomorphometric analysis

For the histometric analysis, the histological sections were photographed and digitized using a light microscope attached to a digital camera (lens magnification, x25) connected to a computer. The fornix of the furcation and root notches were used as reference points. Histometric analysis was conducted using three serial sections representing the central portion of the furcation site (Fernandes et al., 2005). Linear and area measurements were performed using the Jandel Sigma Scan Pro software (Jandel Corporation, San Rafael, CA, USA). The evaluator was blinded to the treatment assigned. The following measurements were performed (Fig. 1F):

1. Total area of the furcation defect (TDA; mm^2)
2. Defect height (DH): the distance between the furcation fornix and the midpoint of a line connecting the notches (mm)
3. Percentage value of the newly formed bone height (NBH): NBH/DH × 100
4. Percentage value of the area of the newly formed bone (NFBA): NFBA/TDA × 100
5. Percentage value of the newly formed cementum (NFAC): length of the NFAC/length of the root from the furcation fornix to the bottom of the notch × 100
6. Percentage value of the newly formed periodontal tissues (NFPL) representing an area coronal to the notch: length of the newly formed PDL/length of the root from the fornix of the furcation to the bottom of the notch × 100
7. Percentage value of the length of the epithelial downgrowth (EP): length of the EP in the defect/length of the root from the fornix of the furcation to the bottom of the notches × 100

2.7. Data analysis

Statistical analysis was done using Statistical Package for Social Science, version 23 (IBM Inc., Chicago, IL, USA). Data are expressed as means and standard deviations. The means were compared using the analysis of variance test. The post-hoc Scheffe test was used for pairwise comparison; p-value < 0.05 was considered statistically significant.

3. Results

The surgical procedures were well tolerated without postoperative complications or infection.

3.1. Histologic and histomorphometric features at one month postoperatively

The histological findings revealed healing represented by newly regenerated thin cylindrical trabeculae of woven bone extending from the base of the defect (notches) to the furcation fornix with wide marrow spaces. The NBH percentage in the HA/ADMA, HA-only, and OFD groups was 52.51%, 49.69%, and 17.72%, respectively (Table 1, Fig. 2A, B, E & G). The NFBA percentage in the HA/ADMA, HA-only, and OFD groups was 48.42%, 45.50%, and 23.53%, respectively (Table 1). The NFAC percentage covering the circumference of the defect in the HA/ADMA, HA-only, and OFD groups was 45.50%, 43.55% and 28.5%, respectively (Table 1). The PDL showed evidence of limited organization, exhibiting distinct fibers with numerous fibroblast cells. The fibers extended approximately 34.50%, 33.1%, and 15.62% of the circumference of the defect in the HA/ADMA, HA-only, and OFD groups, respectively (Table 1). The EP along the furcation defect was not observed in the two test groups. Higher magnification at the notch displayed new attachment and new bone with resting lines (Fig. 2B).

On the OFD group, the defects were filled by granulation tissues with EP along the side of the root, indicating healing by the formation of long junctional epithelium (Fig. 2G). Bone regeneration was limited and restricted to the base of the defect. The NBH, NFBA, NFAC, and NFPL were significantly greater on the test sides than on the control sides ($p < 0.05$); however, no significant differences were observed in histomorphometric parameters between the HA/ADMA and HA-only groups ($p > 0.05$) (Table 2, Fig. 3A).

3.2. Histologic and histomorphometric features at three months postoperatively

The histological findings revealed new highly cellular lamellar bone extending from the base of the defect to the furcation fornix with narrow marrow spaces. The NBH percentage was 90.34%, 88.95%, and 38.55% of the DH in the HA/ADMA, HA-only, and OFD groups, respectively. The NFBA percentage was 83.25%, 80.97%, and 37.5% of the defect area in the HA/ADMA, HA-only, and OFD groups, respectively. A thick amount of new acellular cementum with cementoblasts aligned along the cementum was observed in some areas. The NFAC percentage was 81.83%, 80.70%, and 36.72% of the defect circumferences in the HA/ADMA, HA-only, and OFD groups, respectively (Table 3, Fig. 2C, D, F, &H). The PDL was highly organized, with numerous fibroblast cells. It represented 82.57% and 80.55% of the defect circumferences in the HA/ADMA and HA-only groups, respectively. There was no evidence of EP in the test groups. However, the OFD group showed EP of 8.55% of the defect circumference, the PDL fibers were not organized and occupied 34.50% of the defect circumference (Table 3), and the bone regeneration was less in the middle portion of the defect and pronounced in the lateral part of the specimens (Fig. 2H). Histomorphometric measurements corroborate the histological findings of a reduced NBH percentage. There were significant differences in the histomorphometric parameters between the HA/ADMA and HA-only groups as well as between them and the OFD group. Pairwise comparisons demonstrated significantly greater NBH, NFBA, NFAC, and NFPL in the HA/ADMA group than in the HA-only and OFD groups ($p < 0.05$) (Table 2, Fig. 3B).

4. Discussion

This study was designed to evaluate the potential effects of HA, with or without ADMA, on periodontal regeneration of critical-sized Class II furcation defects created in an animal model. The test sites treated with HA alone or in combination

Table 1 Area and linear measurements of the test and control groups of different tissues in healed furcation defects at one month post-surgically.

	HA/ADMA		HA only		Control group		F (p value)
	Mean ± SD	%	Mean ± SD	%	Mean ± SD	%	
Newly formed bone height (NBH) (mm)	6.43 ± 1.22	52.51	5.98 ± 1.33	49.69	2.53 ± 1.2	17.72	5.284 (0.03)*
Newly formed bone area (NFBA) (mm^2)	6.23 ± 1.41	48.42	5.90 ± 1.43	45.50	2.42 ± 1.62	23.53	5.609 (0.01)*
Newly formed acellular cementum (NFAC) (mm)	5.43 ± 1.21	45.50	5.11 ± 1.41	43.55	2.22 ± 1.3	28.50	4.103 (0.05)*
Newly formed periodontal ligament (NFPL) (mm)	4.32 ± 1.29	34.50	3.95 ± 1.22	33.1	2.24 ± 1.91	15.62	5.299 (0.03)*
Epithelial down growth (mm)	0.0	0.0	0.0	0.0	5.35 ± 1.23	10.25	——

HA = hyaluronic acid, ADMA = Acellular dermal matrix allograft.
F: ANOVA test.
* Significance difference.

with ADMA demonstrated significantly greater amount of newly regenerated tissue than the sites treated with OFD. Moreover, the HA/ADMA group showed significantly higher amounts of NFAC and PDL than the HA group at three months postoperatively. The NFAC in both test groups was the acellular type of varying thickness, covering over 80% of the roots. Moreover, well-organized functionally oriented PDL were observed after three months in both the test groups, as was reported previously (Suaid et al., 2010, Pilloni et al., 2021, Shirakata et al., 2022).

The NFBA was significantly greater in the HA/ADMA and HA-only groups than in the OFD group after three months. A considerable amount of new lamellar bone extending from the base of the defect to the furcation fornix was observed along with numerous osteoblasts and osteoid tissues, and a basophilic line between the bone lamellae lined the newly formed bone. These findings corroborate previous animal studies evaluating the application of β-tricalcium phosphate (Jiang et al., 2010), bovine bone mineral matrix (Suaid et al., 2010), and enamel matrix derivatives (Fernandes et al., 2005) with or without barrier membranes in the furcation defects in dogs. The differences between acute and chronic defects, species, healing time, and materials used should be considered when interpreting these comparisons.

Gengigel® comprises high molecular weight fractions of HA in a 0.8% concentration gel formulation that supports periodontal regeneration and wound healing. The reported outcomes are consistent with previous findings of favorable periodontal regeneration or clinical improvements in probing pocket depth and clinical attachment loss following HA application for intra-bony and gingival recession defects (Pilloni et al., 2021, Shirakata et al., 2021, Shirakata et al., 2022). Positive results were reported by numerous in vitro studies demonstrating the ability of HA to sustain blood clot stability, attract growth factors (Asparuhova et al., 2019, Pilloni et al., 2019), and increase angiogenesis and osteogenesis (Pilloni et al., 2019) while maintaining its fundamental physiochemical and biological properties (Dahiya and Kamal 2013). HA reportedly has bacteriostatic properties and exhibits dose-dependent effects on different microorganisms (Zamboni et al., 2021). Lack of inflammation in the test groups confirmed that both biomaterials are biocompatible, concurring with previous studies (de Andrade et al., 2007, Borges et al., 2009, Matheus et al., 2021).

ADMA is used as a scaffold to promote the regeneration of the host soft tissue (Yaghini et al., 2023). In addition to being an alternative to autogenous soft tissue grafts around teeth and dental implants (Barootchi et al., 2020, Panwar et al., 2022, Zhan et al., 2022, Yaghini et al., 2023), it is used as a barrier membrane in guided-tissue regeneration of furcation defects with results comparable to those of bioabsorbable membranes (de Andrade et al., 2007). It also acts as an effective barrier in GBR for critical-sized defects (Borges et al., 2009) and corrects bone dehiscence and tissue volume loss around dental implants when used as a membrane in addition to bone grafts (Momen-Heravi et al., 2018). ADMA can integrate with the gingival soft tissue and significantly improve the soft tissue dimensions in GBR (Sudarsan et al., 2008).

The test groups did not show EP. Literature confirms that ADMA could prevent epithelial migration and stop the ingrowth of gingival connective tissue in GBR (Borges et al., 2009). It was reported that EP is evident only when partial exposure of the membrane occurs during the early postoperative period because of gingival recession (de Andrade et al., 2007). On the other hand, epithelial and connective tissue ingrowths were observed at all time-points in all the histological sections of the OFD group. The periodontal regeneration amount depends on the available space created and maintained during the healing period (Yang et al., 2022). ADMA acts as a space maintainer and prevents the collapse of the flap into the defect, which could explain the difference in the histomorphometric analysis between the two test groups.

In this study, we surgically created a critical-sized defect in the furcation area. The horizontal and vertical measurements selected for the defect had been previously reported as effective (Pontes et al., 2006, de Andrade et al., 2007). Impression material was used to prevent the spontaneous repair of the defect and facilitated plaque accumulation. Previous studies reported that 14 days were sufficient to induce inflammation and simulate periodontal disease in an animal model (de Andrade et al., 2007). The use of

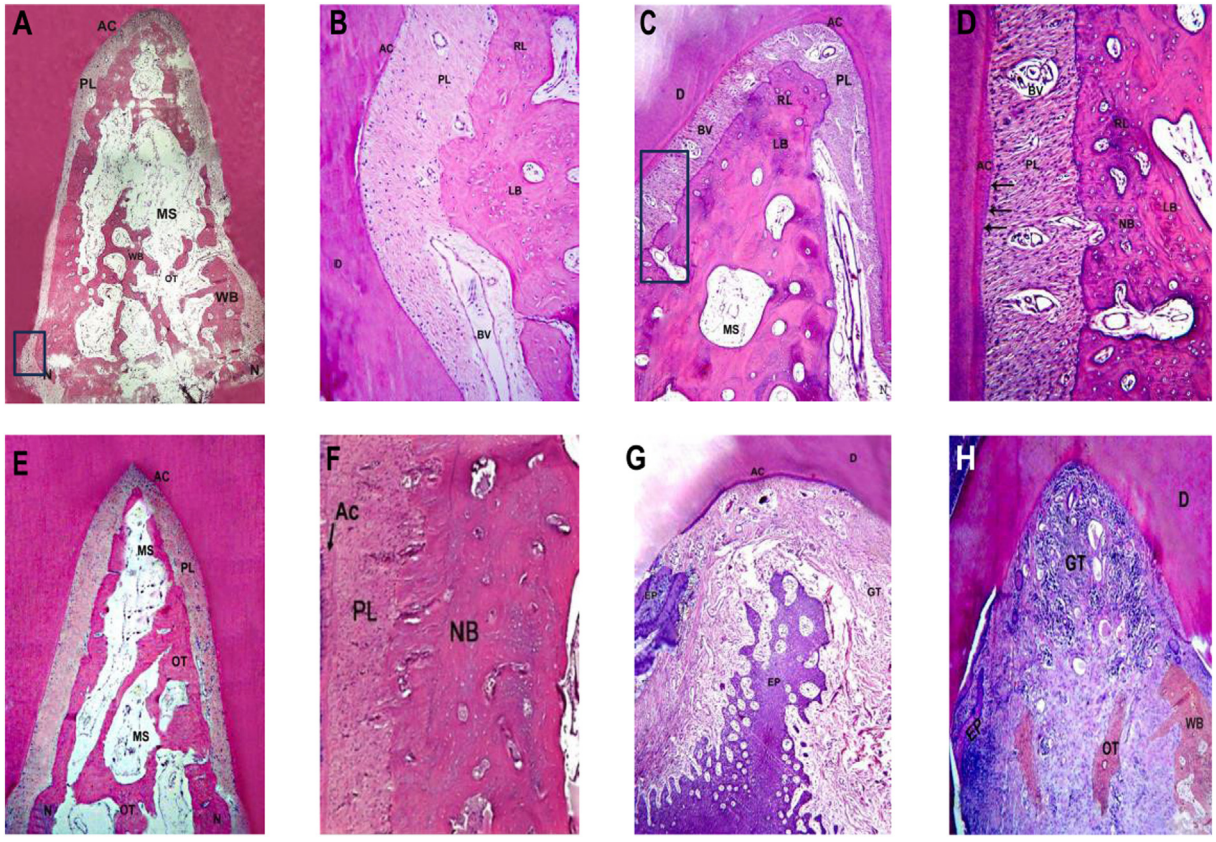

Fig. 2 Hematoxylin & Eosin stained mesiodistal section of furcation defects at one month (A, B, E & G) and three months post-surgically (C, D, F, H). A: **HA & ADMA at one month**, thin cylindrical trabeculae of woven bone extended from the notch to the furcation fornix with wide marrow spaces. B. Higher magnification (x100) of the previous section at the notch area (square) showing thin acellular cementum with cementoblasts, highly vascular and cellular periodontal ligament fibers, and new bone formation with resting lines. C: **HA & ADMA at three months**, a Well-organized periodontal ligament fiber with numerous fibroblast cells, blood vessels, a thick layer of acellular cementum, and newly formed highly cellular lamellar bone with resting lines. D: Higher magnification of the previous section (x200) (square) showing highly cellular and vascular periodontal ligament, lamellar bone with many resting lines, and acellular cementum with cementoblasts (arrows). **E: HA only at one-month,** new bone formation with wide marrow spaces, highly cellular and vascular periodontal ligament. **F: HA only 3 months,** thick acellular cementum, highly cellular vascular periodontal ligament, and new bone formation. **G: Control group at one month,** the control furcation showing granulation tissue with epithelial down growth in the coronal part and along the side of the root. **H: Control group at three months**, granulation tissue, scattered osteoid tissue and woven bone. N: notch, AC: acellular cementum, PL: periodontal ligament, WB: woven bone, LB: lamellar bone, NB: new bone MS: marrow space, RL: resting line, D: dentine, BV: blood vessels, OT: osteoid tissue, GT: granulation tissue, EP: epithelial cells.

Table 2 P values of pairwise comparison using scheffe test between different groups at one and three months post-surgical evaluation.

	HA/ADMA Vs HA only		HA/ADMA Vs Control		HA only Vs Control	
	1 month	3 months	1 month	3 months	1 month	3 months
Bone height (mm)	0.07	0.01*	0.001**	< 0.000**	0.01*	< 0.000**
Bone area (mm^2)	0.06	0.03*	> 0.000**	< 0.000**	0.01*	< 0.000**
Cementum (mm)	0.135	0.02*	0.001**	< 0.000**	0.01*	0.001**
PL (mm)	0.06	0.04*	0.001**	< 0.000**	0.02*	0.001**

HA = hyaluronic acid, ADMA = Acellular dermal matrix allograft, PL = Periodontal ligament.
* Significance difference.
** highly significance.

the mesiodistal sections for the histomorphometric analysis helped evaluate new cementum and PDL formation along the roots and the assessment of the lesion as a whole (Selvig 1994). The split-mouth design limits the biological variability between the animals and further confirms the positive outcomes of the tested biomaterials.

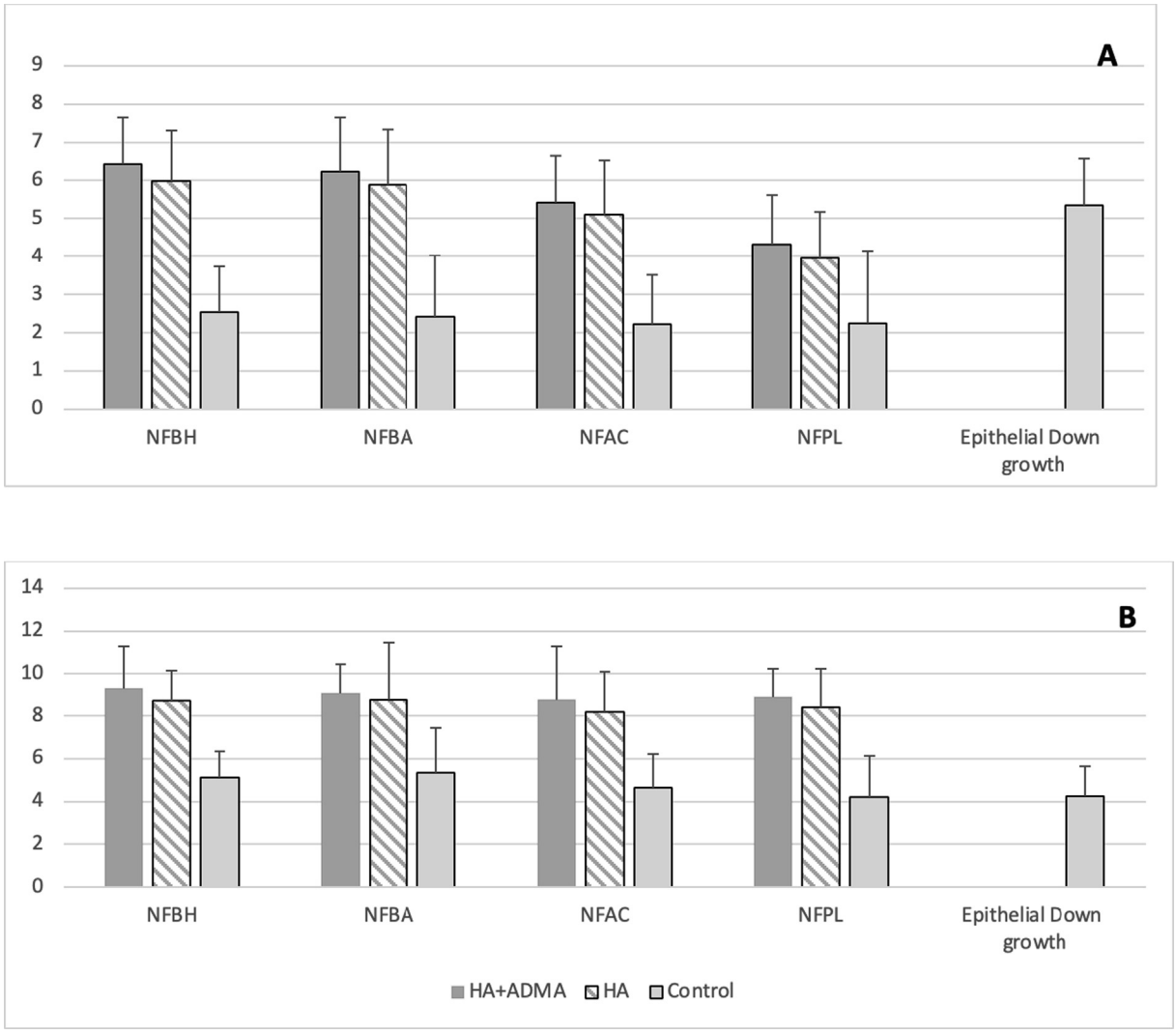

Fig. 3 Mean ± SD of area measurement and linear measurement of the two test and control groups of different tissues in healed defects at one month (**A**) and 3 months (**B**) post-surgically.

Table 3 Area and linear measurements of the test and control groups of different tissues in healed defects at three months post-surgically.

	HA/ADMA		HA only		Control group		F (p value)
	Mean ± SD	%	Mean ± SD	%	Mean ± SD	%	
Newly formed bone height (NBH) (mm^2)	9.34 ± 1.93	90.34	8.72 ± 1.42	88.95	5.11 ± 1.23	38.55	11.326 (0.001)**
Newly formed bone area (NFBA) (mm^2)	9.11 ± 1.34	83.25	8.74 ± 2.71	80.97	5.35 ± 2.10	37.50	19.529 < 0.000**
Newly formed acellular cementum (NFAC) (mm)	8.74 ± 2.56	81.83	8.19 ± 1.92	80.70	4.63 ± 1.6	36.72	7.994 (0.001)**
Newly formed periodontal ligament (NFPL) (mm)	8.92 ± 1.30	82.57	8.42 ± 1.82	80.55	4.21 ± 1.91	34.50	7.327 (0.001)**
Epithelial down growth (EP)(mm)	0.0	0.0	0.0	0.0	4.24 ± 1.42	8.55	–

HA = hyaluronic acid, ADMA = Acellular dermal matrix allograft.
F: ANOVA test.
** Highly significance.

5. Conclusion

The histological and histomorphometric results of this study demonstrate that the use of HA with ADMA positively affects the periodontal regeneration and wound healing in Class II furcation defects.

6. Financial support and sponsorship

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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