Majalah Kedokteran Gigi Indonesia
Vol 11 No 2 – August 2025
ISSN 2460-0164 (print), ISSN 2442-2576 (online)
Available online at https://jurnal.ugm.ac.id/mkgi
DOI: http://doi.org/10.22146/majkedgiind.104632

RESEARCH ARTICLE

The impact of varying concentrations of hyaluronic acid gel on the enhancement of VEGF and angiogenesis expression

Malianawati Fauzia*✉, Ega Lucida Chandra Kumala*, Maulida Aufani, Addini Zoya Syalisha**, Adellia Wahyu**, Muhammad Maulana Zikrullah Mukhlis****

*Department of Periodontics, Faculty of Dentistry, Universitas Brawijaya, Malang, East Java, Indonesia
**Bachelor Degree of Dentistry, Faculty of Dentistry, Universitas Brawijaya, Malang, East Java, Indonesia
*Jl Veteran, Malang, East Java, Indonesia; ✉ correspondence: meli_fkg@ub.ac.id

Submitted: 11st February 2025; Revised: 25th July 2025; Accepted: 6th August 2025

ABSTRACT

Periodontal dressings can contribute to plaque accumulation, which in turn may cause inflammation, irritation of healing tissues, bacteremia, and difficulties in eating. Advances in knowledge and technology have improved the materials used in these dressings, aiming to enhance effectiveness and minimize complications. High-molecular-weight hyaluronic acid (HMW-HA) is a promising dressing material because of its anti-inflammatory properties and its ability to promote epithelial regeneration. This study aimed to determine whether different concentrations of HMW-HA gel influence vascular endothelial growth factor (VEGF) expression and angiogenesis during gingival wound healing in white rats (*Rattus norvegicus*) of the Wistar strain. A total of 42 rats were divided into seven groups: a negative control group (K1), a positive control group (K2) treated with 0.2% Gengigel®, and five treatment groups (P1–P5) receiving HMW-HA gel at concentrations of 0.2%, 0.4%, 0.6%, 0.8%, and 1%, respectively. Standardized 2 mm wounds were created with a punch biopsy on the lower anterior jaw of each rat. Treatments were administered twice daily for seven days. VEGF expression and angiogenesis were evaluated using immunohistochemical and hematoxylin–eosin staining. The group treated with 1% HA gel (P5) showed the highest average VEGF expression and angiogenesis compared with the negative control and lower-concentration treatment groups. These findings suggest that topical application of HMW-HA gel may enhance gingival wound healing in periodontal surgery by promoting angiogenesis and increasing VEGF expression.

Keywords: angiogenesis; HMW-HA; VEGF

INTRODUCTION

The Global Burden of Disease Study (2021) estimated that over 1 billion people are affected by severe periodontitis, with Southeast Asia showing the highest prevalence at 17.57%.[1] In Indonesia, Hijryana et al[2] reported that nearly 75% of older adults had generalized periodontitis, 3% had healthy periodontal status, and approximately 22% had localized periodontitis. In many cases, periodontal surgery is required, resulting in surgical wounds to the periodontal tissue.[3]

Wound healing is a complex and dynamic process aimed at restoring tissue structure and function. It is generally divided into three overlapping phases: inflammation, proliferation, and remodeling. These phases involve coordinated processes of cell migration and proliferation, extracellular matrix synthesis, growth factor signaling, and cytokine activity, leading to tissue restoration.[4]

During the inflammatory phase, macrophages release growth factors such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF). VEGF plays a central role in driving angiogenesis and vascular development, while FGF and VEGF together promote fibroblast proliferation and granulation tissue formation. The application of certain materials can stimulate increased VEGF expression. Natural biomaterials such as hyaluronic acid (HA) are increasingly favored due to their ideal wound-healing characteristics, including biocompatibility, biodegradability, and strong interaction with biological systems. The application of certain materials can stimulate increased VEGF expression. Natural biomaterials such as hyaluronic acid (HA) are increasingly favored due to their ideal wound-healing characteristics, including biocompatibility, biodegradability, and strong interaction with biological systems.[5]

HA is a naturally occurring, non-sulfated glycosaminoglycan that maintains extracellular matrix integrity and tissue hydration. It is classified into high-molecular-weight (HMW-HA) and low-molecular-weight (LMW-HA) forms, each with distinct roles in wound healing.[6] HA enhances fibroblast proliferation, promotes angiogenesis, and regulates cytokine and growth factor expression.

Previous studies have demonstrated the benefits of HA in oral wound healing. Ramadhany et al[7] reported that 0.2% HA gel enhances angiogenesis in gingival wounds in rats. Doğan et al[8] found that 0.6% HA significantly improved healing after frenectomy in pediatric patients. Similarly, de Ramón et al[9] observed superior healing outcomes with 1% HA gel compared to 0.2% in oral mucosal lesions.

However, the effect of different HMW-HA gel concentrations on VEGF expression and angiogenesis in gingival wounds has not been fully established. Therefore, this study aimed to evaluate the impact of various HMW-HA concentrations on VEGF expression and angiogenesis during gingival wound healing in Wistar rats.

MATERIALS AND METHODS

This study was approved by the Animal Care and Use Committee of Universitas Brawijaya, Malang (Ethical Clearance No. 064-KEP-UB-2024). It was conducted as an *in vivo* laboratory experiment using a posttest-only control group design.

The sample size was determined using Federer's formula, resulting in 42 healthy male Wistar rats (*Rattus norvegicus*), each weighing 180–250 g. The rats were randomly assigned to seven groups (n = 6 per group). The negative control group (K1) received no treatment, the positive control group (K2) was treated with 0.2% Gengigel® (Gengigel, Ricerfarma, Milano, Italy), and the remaining five treatment groups (P1–P5) received high-molecular-weight hyaluronic acid (HMW-HA) gel at concentrations of 0.2%, 0.4%, 0.6%, 0.8%, and 1%, respectively.

HMW-HA powder (1200 kDa; ECOORI PTE LTD, Singapore) was formulated into gel at the Pharmacy Laboratory, Ma Chung University, Malang, Indonesia. Viscosity, spreadability, mucoadhesiveness, and stability tests were performed, and toxicity testing was conducted at the Pusvetma Laboratory, Surabaya, Indonesia. All concentrations exhibited good stability, viscosity, spreadability, and mucoadhesiveness, and were found to be non-toxic. The animals were acclimatized for seven days prior to surgery. Anesthesia was administered via intramuscular injection of a ketamine–xylazine combination in a 1:1 ratio at a dose of 100 mg/mL. A standardized wound measuring 2 mm in diameter and 1 mm in depth was created 2 mm below the cervical margin of the left lower incisor using a Ribbel Disposable Dermal Biopsy Punch® (India). The wound was rinsed with 0.9% NaCl solution before treatment application. In the negative control group, the wound was left untreated; in the positive control group, the wound was treated with 0.2% Gengigel®; and in the treatment groups, the wounds were treated with the respective concentrations of HMW-HA gel. A total of 0.05 mL of gel was applied to the wound area using a syringe twice daily for seven days.

At the end of the treatment period, the animals were sacrificed via cervical dislocation.[10] The gingival granulation tissues were fixed in 10% formalin solution, placed in labeled containers according to each group, and processed for paraffin embedding to facilitate thin sectioning. Deparaffinization was performed using xylol (MERCK, 18.661.500, Germany), followed by rehydration through graded ethanol solutions (MERCK, 1.009.832.500, Germany) down to distilled water. Antigen retrieval was carried out by heating the preparations in a microwave for 10 minutes. Anti-VEGF antibody (SIGMA ALDRICH, ABS82, Germany) was applied to bind to the target antigen.

The preparations were rinsed with buffer for 3 minutes, repeated three times, and gently dried with absorbent paper. The HRP (horseradish peroxidase)-conjugated secondary antibody (biotinylated goat anti-mouse IgG and goat anti-rabbit IgG; IHC Select® HRP/DAB kit, Germany) was applied and incubated at 37 °C for 30 minutes. DAB substrate (IHC Select® HRP/DAB kit, Germany) was then applied dropwise to the tissue sections. Counterstaining was performed by immersing the slides in Harris hematoxylin (LEICA, 3801570, Germany) for 30–60 seconds, followed by rinsing in water, differentiation in alcohol with 1% HCl, another water rinse, dehydration in ethanol (MERCK, 1.009.832.500, Germany), and clearing in xylol (MERCK, 18.661.500, Germany). The preparations were then mounted with a cover glass (ONE LAB, China).

For hematoxylin and eosin (H&E) staining, the preparations were fixed in cold methanol at –20 °C for 3–5 minutes, rinsed in water and PBS (Biogear, BGPBS-002, China), and stained with hematoxylin (LEICA, 3801570, Germany) for 5–7 minutes. Slides were then dipped 20 times in eosin (LEICA, 3801602, Germany), dehydrated in ethanol, rinsed in PBS, cleared in xylol (MERCK, 18.661.500, Germany), and mounted with cover glass (ONE LAB, China). After drying, the preparations were ready for microscopic examination.

Histopathological evaluation was performed by counting angiogenic vessels in five fields of view (LP) at 400× magnification using a Nikon Eclipse type Ei® light microscope (USA) equipped with an Optilab® SIGMA microscope camera (MTN02024, Indonesia) connected to a computer. The counts were averaged for each sample. Angiogenic vessels were identified as irregularly shaped structures, sometimes with incomplete endothelial cell linings. Endothelial cell nuclei stained blue with hematoxylin, whereas cytoplasm and surrounding tissues stained pink with eosin.

IHC preparations were examined under a Nikon Eclipse Ei microscope at 40× and 10× magnifications to assess staining intensity and patterns. Image analysis was conducted using the IMAGE-J software as follows: open the application, load the selected image according to the field of view, select “image” → “type” (16-bit), adjust settings, and set the threshold to determine color intensity percentage. Processed data were then exported to Microsoft Excel for further analysis.

All data are expressed as mean ± standard deviation (mean ± SD) for each group. Angiogenesis data were not normally distributed (Shapiro–Wilk $p \leq 0.05$) and were analyzed using the Kruskal–Wallis test followed by the Mann–Whitney post hoc test. VEGF expression data were normally distributed (Shapiro–Wilk $p > 0.05$) and analyzed using ANOVA followed by Tukey’s HSD post hoc test. Statistical analyses were conducted using SPSS for Windows, version 21.0 (SPSS Inc., Chicago, IL, USA), with statistical significance set at $p < 0.05$.

RESULTS

VEGF is expressed by macrophages, appearing brownish upon binding with anti-VEGF antibodies. In the control groups, the positive control group (K2) exhibited a higher mean VEGF expression compared with both the negative control and the treatment groups. Among the treatment groups, the highest mean VEGF expression was observed in the group receiving 1% HA gel (P5). Overall, the lowest mean VEGF expression was recorded in the negative control group (K1), which received no treatment.

In H&E-stained preparations, endothelial cells forming the walls of blood vessels appeared reddish-brown, whereas surrounding tissues stained blue (hematoxylin) and pink (eosin). The negative control group had the lowest mean vessel count among all groups. In the treatment groups, the average number of new blood vessels increased progressively with higher HMW-HA gel concentrations, with P5 (1% HMW-HA gel) exhibiting the highest value. The positive control group had the highest mean number of new vessels overall.

The negative control group (K1) differed significantly from all other groups except P1 (0.2% HMW-HA gel). The positive control group (K2) showed significant differences compared with K1 and all treatment groups (P1–P4) but not with P5 (1% HMW-HA gel).

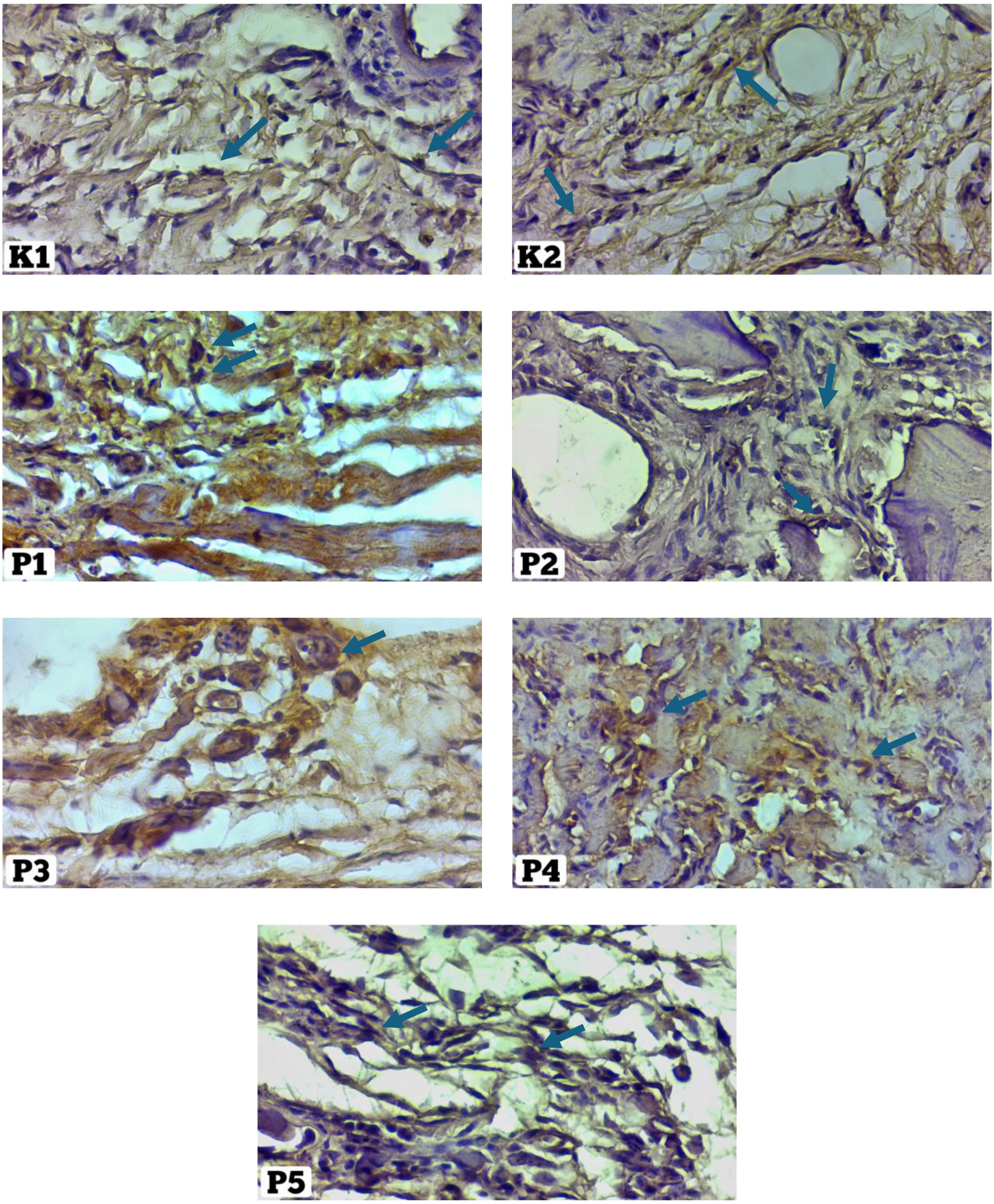

Figure 1. VEGF expression (green arrows) in the control and treatment groups on IHC staining. VEGF expression was assessed based on the staining intensity in endothelial cells compared with epithelial cells. Brown cytoplasmic staining in epithelial cells was interpreted as positive VEGF expression

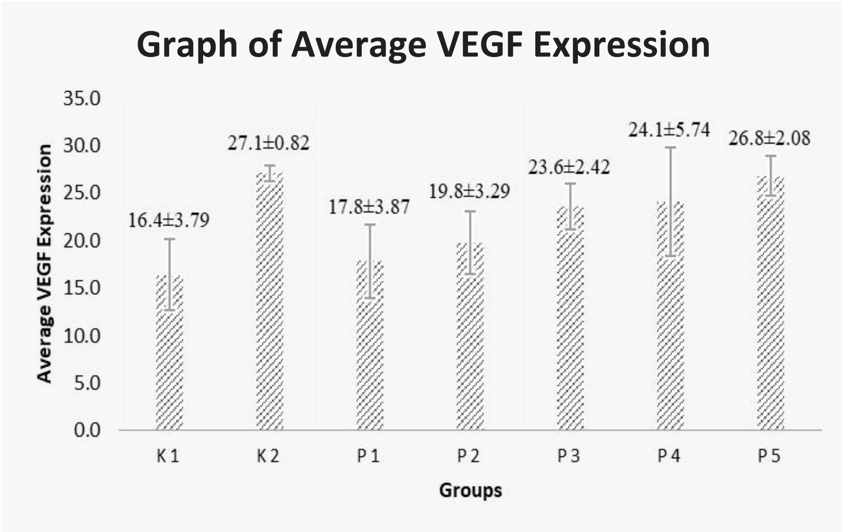

Figure 2. Average of VEGF expression by macropage cells

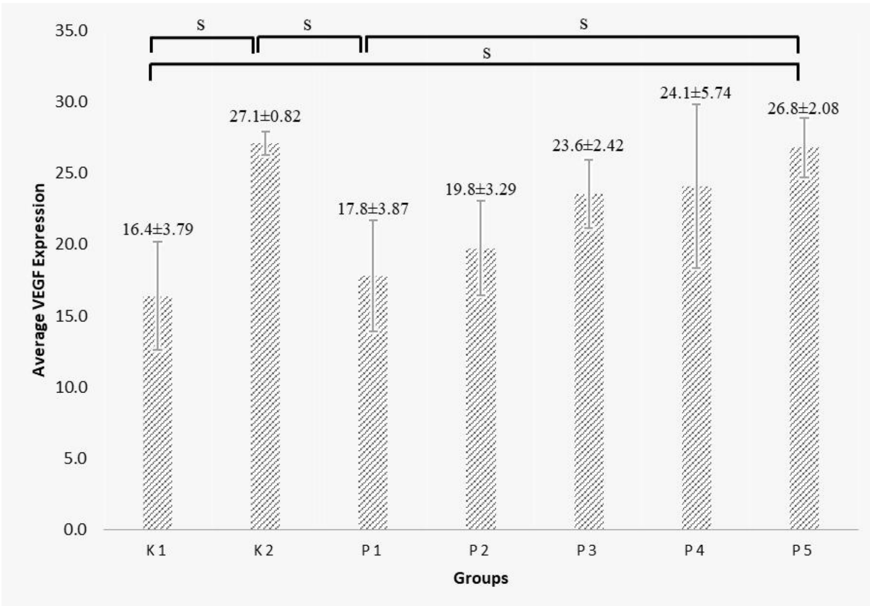

Figure 3. Results of Tukey's HSD test for VEGF expression (s = significant). The post hoc analysis revealed significant differences between K1 and K2, K1 and P5, K2 and P1, and P1 and P5

DISCUSSION

VEGF is a key growth factor in the wound healing process, produced by various cells involved in tissue repair, with macrophages being among the primary sources. As a potent regulator of angiogenesis, VEGF stimulates endothelial cell proliferation and the formation of new blood vessels, which are essential for delivering nutrients to developing granulation tissue.[11] Several studies have demonstrated that VEGF expression is upregulated during the first 10 days following injury, peaking between days 5 and 10 in rat models.[12]

Wound healing begins immediately after injury. Within seconds, hemostasis occurs through clot formation. During the inflammatory phase (24–36 hours post-injury), neutrophils arrive to

Majalah Kedokteran Gigi Indonesia. Agustus 2025; 11(2): 115-125
ISSN 2460-0164 (print)
ISSN 2442-2576 (online)

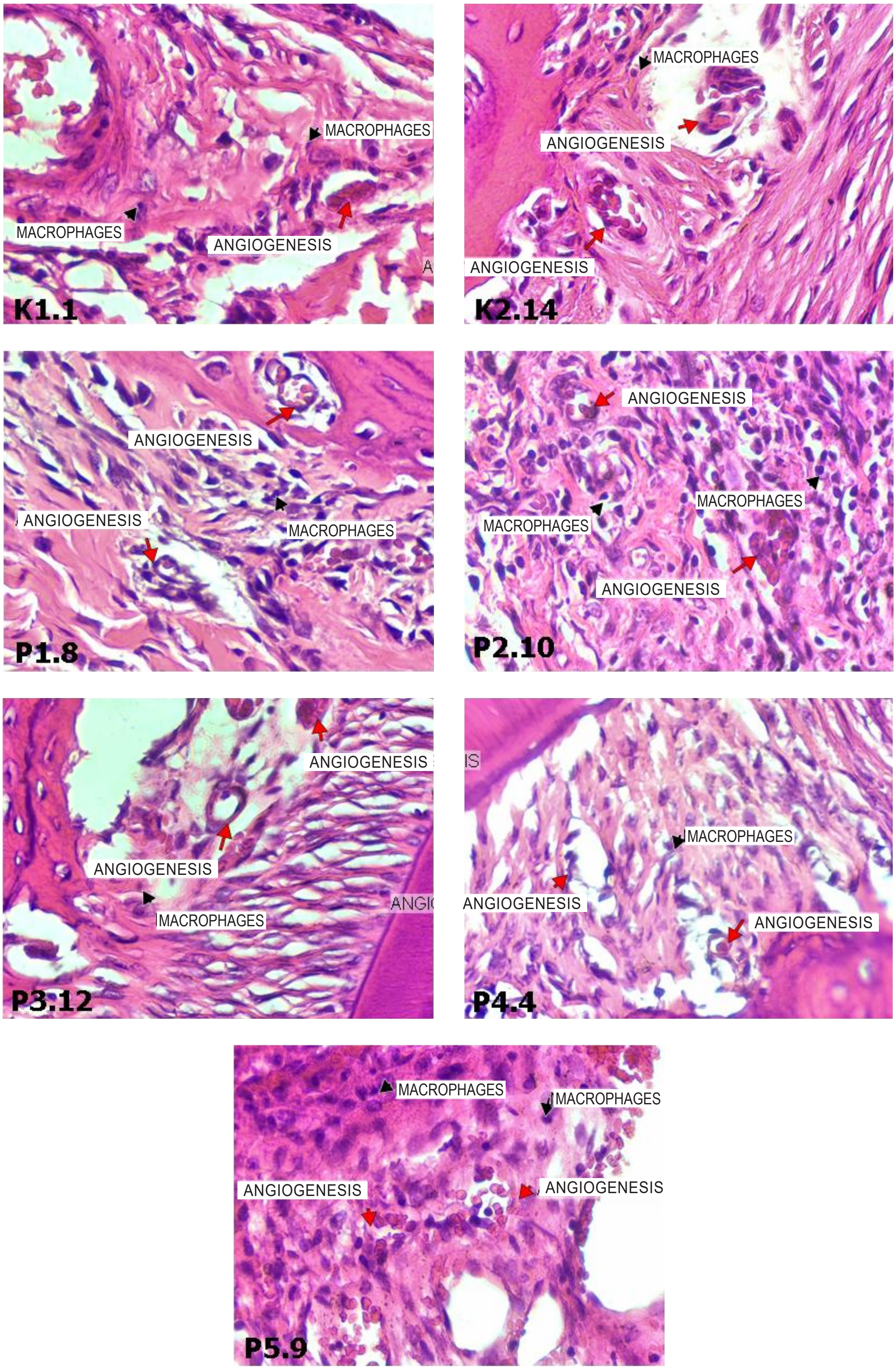

Figure 4. Angiogenesis observed in the positive control group (K2) and the treatment groups (P1–P5) was more prominent than in the negative control group (K1)

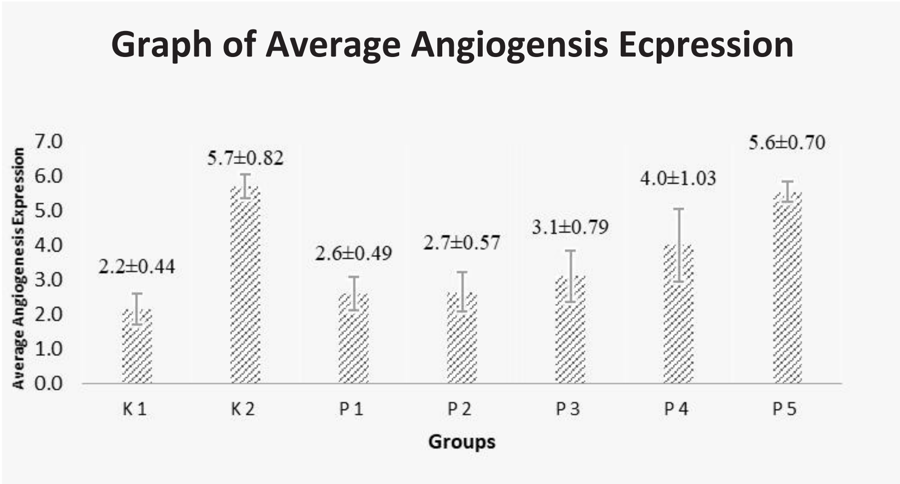

Figure 5. Average number of new blood vessels in the control and treatment group

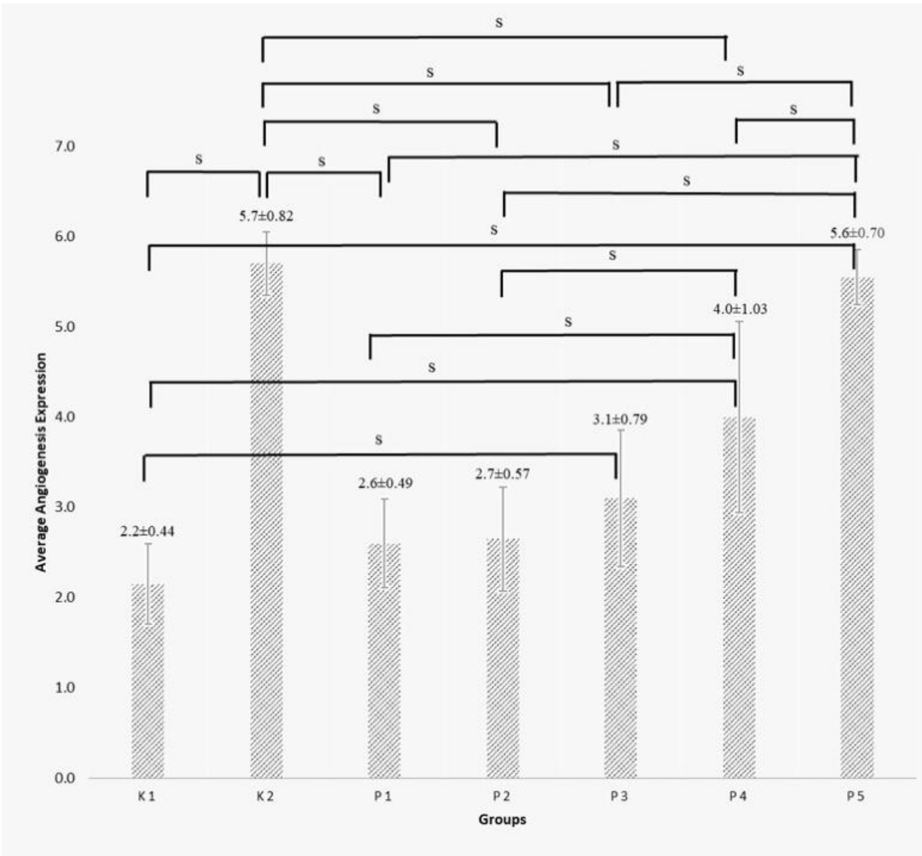

Figure 6. Comparison of the mean angiogenesis levels between groups (s = significant)

perform phagocytosis and eliminate bacteria. At 48–72 hours, macrophages replace neutrophils, continuing phagocytosis and releasing multiple growth factors. The subsequent proliferation phase is marked by granulation tissue formation, angiogenesis, and re-epithelialization. This regeneration is promoted by pro-regenerative M2 macrophages, which release growth factors

Majalah Kedokteran Gigi Indonesia. Agustus 2025; 11(2): 115-125
ISSN 2460-0164 (print)
ISSN 2442-2576 (online)

such as FGF, EGF, and VEGF. This phase can last up to three weeks. Fibroblasts migrate to the wound site in response to PDGF released by platelets, synthesizing new extracellular matrix (ECM). TGF-β1 then stimulates fibroblasts to produce collagen, supporting re-epithelialization. In the final remodeling and maturation phase, granulation tissue is reorganized, and endothelial cells, macrophages, and myofibroblasts undergo apoptosis. These processes result in scar tissue formation, signaling the completion of the wound healing process.[13]

The increase in VEGF expression observed in this study supports the notion that VEGF plays a critical role in the wound healing process, consistent with the findings of Cahyati, who reported significantly higher mean VEGF expression in treatment groups compared with controls. This effect can be triggered by the administration of biomaterials such as hyaluronic acid (HA), which has been demonstrated in numerous studies to promote the healing of full-thickness surgical wounds. HA is believed to facilitate re-epithelialization, leading to the formation of soft tissues and increased microvascular density.[14]

In addition to its regenerative potential, HA can serve as a stable barrier against viral and bacterial penetration due to its viscoelastic properties. It also exhibits a bacteriostatic effect, which is particularly beneficial in post-surgical wounds to prevent contamination by pathogens and reduce the risk of postoperative infection, thereby improving healing predictability.[15] Hong et al reported findings that support the present results, showing that the topical application of HA to skin wounds increased VEGF expression, with the peak observed on day 7 compared with controls.[16] Similarly, Bonatto et al. demonstrated that HA gel combined with green tea enhanced VEGF expression in post-extraction wounds.[17] Canciani et al further showed that the application of 1.2% low-molecular-weight HA gel to oral mucosal wounds promoted new blood vessel formation.[18]

Yang et al described HA as a polymer compound with the capacity to enhance wound healing by stimulating the production of regenerative cells, including growth factors.[19] Asparuhova et al provided additional evidence, showing that high-molecular-weight HA (HMW-HA) gel promotes fibroblast proliferation in gingival and palatal mucosa while upregulating gene expression for growth factors.[6] Hwang and Lee similarly noted that HA gel can induce growth factor production by modifying its physical and chemical properties, including HA concentration.[20]

Multiple studies have confirmed the efficacy of HA in wound healing. For example, Canciani et al (2021) reported that HA gel, when combined with other agents, improved healing in oral mucosal wounds.[18] Gupta (2017) also found that 0.8% HA was effective in treating grade II furcation defects after flap surgery, as demonstrated by defect closure.[21]

In the present study, the highest mean VEGF expression and angiogenesis levels were observed in the group treated with 1% HA gel. This aligns with the findings of Al-Saadi and Al-Quisi (2023), who reported that 1% HA gel significantly reduced postoperative pain, trismus, and edema compared with controls following mandibular third molar surgery. This effect may be attributed to the higher viscosity of concentrated HMW-HA gels.[22] HA with greater molecular weight and concentration exhibits higher viscosity,[23] as demonstrated in previous studies showing that a twofold increase in HA concentration or molecular weight can result in up to a tenfold change in viscosity. This occurs because concentration reflects the number of solute particles per unit volume; a greater particle density increases interparticle friction, thereby raising viscosity. This property may explain the marked difference in VEGF expression between the 1% HA gel and the 0.2% HA gel groups in this study.[24]

A notable finding was the significant difference between the 0.2% HA gel group and the positive control group, despite both containing 0.2% HA. The commercial product used in the positive control group (Hyaluronic Acid 0.2% + Xylitol + Dichlorobenzyl Alcohol) had a viscosity of 1,000 dPas, compared with 37–110 dPas for the formulated HA gel. Additionally, the commercial product used HMW-HA with a molecular weight of

1.5 MDa, whereas the experimental gel contained HMW-HA of 1 MDa.[25] Although both are classified as HMW-HA, their molecular weights differ, and this difference can influence biological activity. Kawano (2021) noted that the binding affinity of HA to the CD44 receptor in fibroblasts increases with molecular weight, conferring greater resistance to dissociation. CD44, a primary HA receptor, promotes cell proliferation, differentiation, migration, and the induction of inflammatory cytokines or matrix metalloproteinases (MMPs) upon binding with HA.[26] In this study, the combination of 0.2% HA, xylitol, and dichlorobenzyl alcohol in the commercial product may have enhanced CD44 clustering, resulting in significantly higher VEGF expression compared with both the P1 group and the negative control (K1).

The formulation containing 0.2% hyaluronic acid, xylitol, and dichlorobenzyl alcohol incorporates additional components that enhance its therapeutic profile. Specifically, 2,4-dichlorobenzyl alcohol contributes antibacterial and antiseptic properties, while xylitol serves as a sweetening agent to improve palatability. Although clinical studies have demonstrated the safety of this formulation with minimal adverse effects, the inclusion of methanol presents potential toxicological concerns, particularly with respect to visual impairment. The synergistic interaction of these adjuvant compounds with the inherent antibacterial properties of hyaluronic acid appears to amplify antimicrobial efficacy. This pharmacological potentiation may explain the observed elevation in VEGF expression in the group treated with 0.2% hyaluronic acid combined with xylitol and dichlorobenzyl alcohol compared with the 1% HA gel monotherapy group. However, statistical analysis revealed no significant difference between these two treatment modalities.[25]

This study acknowledges several methodological limitations. First, the experimental design was constrained by a maximum hyaluronic acid concentration of 1%, which may not fully capture the dose–response relationship or identify the optimal therapeutic concentration. Second, temporal assessment was limited to a single time point, with specimen collection conducted exclusively on day 7 post-treatment. Future research should include a wider concentration range to determine the maximum tolerated dose and establish toxicity thresholds. Additionally, incorporating multiple sacrifice time points during the experimental period would allow for a more comprehensive temporal analysis of neovascularization dynamics and VEGF expression patterns, thereby generating more robust kinetic data on the angiogenic response to hyaluronic acid therapy.

CONCLUSION

This study demonstrates that increasing the concentration of HMW-HA gel enhances VEGF expression and promotes angiogenesis during gingival wound healing in Wistar strain white rats (*Rattus norvegicus*).

ACKNOWLEDGMENT

This work was supported by funding from the Faculty of Dentistry, Universitas Brawijaya.

Conflict of interest

The authors declare no conflicts of interest related to this study.

REFERENCES

1. Nascimento GG, Alves-Costa S, Romandini M. Burden of severe periodontitis and edentulism in 2021, with projections up to 2050: the global burden of disease 2021 study. J Periodontal Res. 2024; 59(5): 823-867. doi: 10.1111/jre.13337
2. Hijryana M, MacDougall M, Ariani N, Saksono P, Kusdhany LS, Walls AWG. Periodontal disease and oral health–related quality of life in the older population in Indonesia. JDR Clin Trans Res. 2022; 7(3): 277–288. doi: 10.1177/23800844211021391
3. Suryono S, Yassa RM, Saputro LT, Walianto AP, Seno Aji NRA. Antibacterial potential from

periodontal dressing raw propolis Trigona itama bee based against Porphyromonas gingivalis: experimental research. Jurnal Kedokteran Gigi Universitas Padjadjaran. 2023; 35(1): 6-13. doi: 10.24198/jkg.v35i1.46229
4. Kathariya R, Jain H, Jadhav T. To pack or not to pack: the current status of periodontal dressings. J Appl Biomater Funct Mater. 2015; 13(2): 73–86. doi: 10.5301/jabfm.5000215
5. Dias Moreira T, Martins V, da Silva Júnior A, Sayer C, Araújo P, Immich A. New insights into biomaterials for wound dressings and care: Challenges and trends. Prog Org Coat. 2024; 187: 108118. doi: 10.1016/j.porgcoat.2023.108118
6. Asparuhova MB, Kiryak D, Eliezer M, Mihov D, Sculean A. Activity of two hyaluronan preparations on primary human oral fibroblasts. J Periodontal Res. 2019; 54(1): 33–45. doi: 10.1111/jre.12602
7. Ramadhany EP, Ambarawati IGAD, Musyaffa MR. Effect of 4% and 15% moringa leaf extract gel on gingival wound healing in rats. Majalah Kedokteran Gigi Indonesia. 2023; 8(3): 192-199. doi: 10.22146/majkedgiind.76416
8. Doğan SSA, Karakan NC, Doğan Ö. Effects of topically administered 0.6% hyaluronic acid on the healing of labial frenectomy in conventional and 940-nm indium gallium arsenide phosphide (InGaAsP) diode laser techniques in pediatric patients: a randomized, placebo-controlled clinical study. Lasers Med Sci. 2024; 39(1): 48. doi: 10.1007/s10103-024-03983-7
9. Ripollés de Ramón Calle Platerías J. Pilot clinical study of the efficacy of a hyaluronic acid (1%) and chlorhexidine (0.20%) gel in post-extraction dentistry. Cientifica Dental. 2021; 17: 4-11.
10. Muche-Borowski C, Selbmann H, Nothacker M, Müller W, Kopp I. AWMF guidance manual and rules for guideline development. Version 2.1; 2023. 91
11. Rujirachotiwat A, Suttamanatwong S. Curcumin upregulates transforming growth factor-β1, its receptors, and vascular endothelial growth factor expressions in an in vitro human gingival fibroblast wound healing model. BMC Oral Health. 2021; 21(1): 535. doi: 10.1186/s12903-021-01890-9
12. De la Riva B, Sánchez E, Hernández A, Reyes R, Tamimi F, López-Cabarcos E, et al. Local controlled release of VEGF and PDGF from a combined brushite–chitosan system enhances bone regeneration. J Control Release. 2010; 143(1): 45–52. doi: 10.1016/j.jconrel.2009.11.026
13. Leśków N, Karp Z, Banaszewski M, Popielska K, Grześkowiak M, Mikołajski J, et al. Characteristics and cellular mechanism of the wound healing process in the oral mucosa. Medical Journal of Cell Biology. 2023; 11(1): 1–12. doi: 10.2478/acb-2023-0001
14. Ayu Wulan Sari D, Cahyati M. Pengaruh gel ekstrak daun kersen (Muntingia calabura L.) terhadap ekspresi VEGF pada penyembuhan luka pasca pencabutan gigi tikus (Rattus norvegicus). E-Prodenta Journal of Dentistry. 2024; 8(1): 123–132.
15. Valachová K, Šoltés L. Hyaluronan as a prominent biomolecule with numerous applications in medicine. Int J Mol Sci. 2021; 22(13): 7077. doi: 10.3390/ijms22137077
16. Hong L, Shen M, Fang J, Wang Y, Bao Z, Bu S, et al. Hyaluronic acid (HA)-based hydrogels for full-thickness wound repairing and skin regeneration. J Mater Sci Mater Med. 2018; 29(9): 150. doi: 10.1007/s10856-018-6158-x
17. Bonatto M da S, Feltran G da S, Barbosa TP, Pereira DA, Santos S de S, Mendes PGJ, et al. Green tea and hyaluronic acid gel enhance fibroblast activation and improves the gingival healing post-third molar extraction. Sci Rep. 2024; 14(1): 7124. doi: 10.1038/s41598-024-57821-5
18. Canciani E, Sirello R, Pellegrini G, Henin D, Perrotta M, Toma M, et al. Effects of vitamin and amino acid-enriched hyaluronic acid gel on the healing of oral mucosa: in vivo and in vitro study. Medicina (B Aires). 2021; 57(3): 285. doi: 10.3390/medicina57030285

19. Yang H, Song L, Zou Y, Sun D, Wang L, Yu Z, et al. Role of hyaluronic acids and potential as regenerative biomaterials in wound healing. ACS Appl Bio Mater. 2021; 4(1): 311–324. doi: 10.1021/acsabm.0c01364
20. Hwang HS, Lee CS. Recent progress in hyaluronic-acid-based hydrogels for bone tissue engineering. Gels. 2023; 9(7): 588. doi: 10.3390/gels9070588
21. Gupta S. Evaluation of gengigel® application in the management of furcation with coronally advanced flap through surgical re-entry- a split mouth clinical study. J Clin Diagn Res. 2017; 11(1): ZC27-ZC32. doi: 10.7860/JCDR/2017/21938.9169
22. Al-Saadi TS, Al-Quisi AF. The influence of the hyaluronic acid gel on the postoperative sequelae following surgical removal of the impacted mandibular third molar in comparison with the A-PRF: a randomized controlled trial. Int J Biomater. 2023; 2023: 1–7. doi: 10.1155/2023/1883460
23. Kim YJ, Carvalho FC, Souza JA, Gonçalves PC, Nogueira AV, Spolidório LC, Roque-Barreira MC, Cirelli JA. Topical application of the lectin Artin M accelerates wound healing in rat oral mucosa by enhancing TGF-β and VEGF production. Wound Repair Regen. 2013; 21(3): 456-463. doi: 10.1111/wrr.12041.
24. Snetkov P, Zakharova K, Morozkina S, Olekhnovich R, Uspenskaya M. Hyaluronic acid: the influence of molecular weight on structural, physical, physico-chemical, and degradable properties of biopolymer. Polymers (Basel). 2020; 12(8): 1800. doi: 10.3390/polym12081800
25. Jain Y. Clinical evaluation of 0.2% hyaluronic acid containing gel in the treatment of gingivitis. Medical Journal of Dr D.Y. Patil University. 2013; 6(4): 416-420. doi: 10.4103/0975-2870.118296
26. Kawano Y, Patrulea V, Sublet E, Borchard G, Iyoda T, Kageyama R, et al. Wound healing promotion by hyaluronic acid: effect of molecular weight on gene expression and in vivo wound closure. Pharmaceuticals. 2021; 14(4): 301. doi: 10.3390/ph14040301