ORIGINAL RESEARCH ORİJİNAL ARAŞTIRMA

DOI: 10.5336/dentalsci.2024-104539

Investigation of the Efficacy of Hypochlorous Acid as a Postoperative Wound Antiseptic: A Randomized Controlled Pilot Study

Postoperatif Yara Antiseptiği Olarak Hipokloröz Asidin Etkinliğinin İncelenmesi: Randomize Kontrollü Pilot Çalışma

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ABSTRACT Objective: This study aims to investigate the effectiveness of hypochlorous acid (HA) as a postoperative wound antiseptic in patients undergoing gingivectomy. **Material and Methods:** Twenty four patients who were diagnosed with chronic inflammatory gingival overgrowth were included in the study. After the gingivectomy procedure, patients were randomly divided into 3 groups according to the mouthwash they used for postoperative wound care; 1) HA group, 2) Chlorhexidine (CHX) group, 3) Saline (control) group. Records of the operation area were taken at the beginning, on the 1st, 3rd and 7th days. Periodontal indexes, visual analog scale (VAS), hydrogen peroxide (H_2O_2), plaque staining agent test, and histological analyzes were used to evaluate wound healing. The data were analyzed statistically. **Results:** The HA and CHX groups were statistically significantly lower than the control group in the plaque index and bleeding on probing values measured on the 7th day ($p<0.05$). There was no statistically significant difference between groups in VAS and H_2O_2 test ($p>0.05$). In the staining agent test, no statistically significant difference was found between control days in all groups and between the groups. In the histological analysis, statistically significantly more keratinocyte cells were found in the HA group than both groups in the samples taken on control days ($p<0.05$). **Conclusion:** HA has been histologically proven to support wound healing after periodontal surgery. HA can be recommended as a good alternative to CHX for postoperative wound care.

Keywords: Antiinfective agents; gingival overgrowth; gingivectomy; hypochlorous acid; wound healing

ÖZET Amaç: Bu çalışma, gingivektomi yapılan hastalarda postoperatif yara antiseptiği olarak hipokloröz asidin (HA) etkinliğini araştırmayı amaçlamaktadır. **Gereç ve Yöntemler:** Kronik inflamatuar diş eti büyümesi tanısı alan 24 hasta çalışmaya dâhil edildi. Gingivektomi işlemi sonrasında hastalar postoperatif yara bakımında kullandıkları gargaralara göre rastgele 3 gruba ayrıldı; 1) HA grubu, 2) Klorheksidin [Chlorhexidine (CHX)] grubu, 3) Salin (kontrol) grubu. Başlangıçta, 1, 3 ve 7. günde operasyon bölgesinin kayıtları alındı. Yara iyileşmesini değerlendirmek için periodontal indeksler, görsel analog skala [visual analog scale (VAS)], hydrogen peroxide (H_2O_2), plak boyayıcı ajan testi ve histolojik analizler kullanıldı. Veriler istatistiksel olarak analiz edildi. **Bulgular:** Yedinci günde ölçülen plak indeksi ve sondalamada kanama değerlerinde HA ve CHX grupları kontrol grubuna göre istatistiksel olarak anlamlı derecede düşüktü ($p<0,05$). VAS ve H_2O_2 testinde gruplar arasında istatistiksel olarak anlamlı fark yoktu ($p>0,05$). Plak boyama ajanı testinde tüm gruplarda kontrol günleri arasında ve gruplar arasında istatistiksel olarak anlamlı fark bulunamadı ($p>0,05$). Histolojik analizde kontrol günlerinde alınan örneklerde HA grubunda her iki gruba göre istatistiksel olarak anlamlı düzeyde daha fazla keratinosit hücresi tespit edildi ($p<0,05$). **Sonuç:** Periodontal cerrahi sonrası, HA'nın yara iyileşmesini desteklediği histolojik olarak kanıtlanmıştır. Postoperatif yara bakımında CHX iyi bir alternatif olarak HA önerilebilir.

Anahtar Kelimeler: Antienfektif ajanlar; dişeti büyümesi; gingivektomi; hipokloröz asit; yara iyileşmesi

Gingival overgrowth is characterized by increased gingival volume; caused by several diseases such as systemic diseases, drug use, inflammation, and neoplastic conditions.[1] Gingival hypertrophy is most commonly encountered due to chronic inflammation of the gingival tissue caused by bacterial

TO CITE THIS ARTICLE:
Sevinç Gül SN, Güzel BZ, Çögenli DR, Pekince Özöner M, Dilsiz A. Investigation of the efficacy of hypochlorous acid as a postoperative wound antiseptic: A randomized controlled pilot study. Turkiye Klinikleri J Dental Sci. 2025;31(2):233-40.

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Peer review under responsibility of Turkiye Klinikleri Journal of Dental Sciences.

Received: 25 Jun 2024 ***Received in revised form:*** 06 Jan 2025 ***Accepted:*** 03 Feb 2025 ***Available online:*** 22 Apr 2025

plaque.[2] Gingival enlargements are treated with gingivectomy and gingivoplasty, and then the incision site occurs with secondary wound healing.[3]

Microbial infection at the surgical site can hinder tissue's natural healing process.[4] The reduced risk of postoperative infection of the injured area is directly related to meticulous plaque control in the early postoperative phase.[5]

Mechanical plaque removal with a toothbrush, interdental brushes, or dental floss is vital to maintaining periodontal and dental health. However, due to patient pain and the danger of possible tissue trauma, mechanical oral hygiene is limited for the first 7-10 days following surgery.[6] Therefore, chemical suppression of plaque becomes important.

One of the main factors affecting the success after the operation is the amount of wound healing.[7] Mechanical plaque control is difficult during this period and is sometimes not recommended immediately after surgery. As a result, oral hygiene can be neglected.[8] It is crucial to practice good oral hygiene and plaque control at the surgical site, as dental plaque has a detrimental effect on wound healing.[9] Since mechanical plaque control is difficult to achieve following oral surgery, chemical agents are often utilized to prevent or reduce dental plaque formation and reduce inflammation to ensure normal healing.[10] It has been reported that antimicrobial mouthwashes can accelerate gingival healing after surgery.[11]

Although chlorhexidine (CHX) is considered the gold standard, the search for alternative plaque control methods continues. New oral antimicrobial drugs are needed for oral usage, as CHX's unfavorable side effects and possible bacterial resistance are major concerns.

With a broad spectrum of bacteria, hypochlorous acid (HA) in the form of a physiologically stable solution demonstrates strong antimicrobial properties, as shown in numerous studies.[12-14] HA is a physiological substance synthesized in neutrophil phagolysosomes during phagocytosis, and since its pH is compatible with body and blood pH; The absence of a cytotoxic effect in contact with all mucosae in the body, including the mouth, gums, throat, nose, mediastinum, peritoneum, eye and eyelid, makes HA an attractive option as a surgical wound area antiseptic, especially in medical procedures.[15]

Although there have been studies on HA in other fields of medicine, no study has been found investigating its effectiveness on wound healing after periodontal surgery. This study aims to clinically and histologically investigate the effect of HA on postoperative wound care in patients who underwent gingivectomy.

MATERIAL AND METHODS

STUDY POPULATION

This study was approved by the Clinical Research Ethics Committee of Atatürk University Faculty of Medicine with the decision numbered 2/114 dated March 30, 2023. The Principles of the Declaration of Helsinki conducted it and registered at the ClinicalTrials.gov (Identifier: NCT06760403). This study included 24 systemically healthy individuals aged 12-30 with chronic inflammatory gingival overgrowth (Figure 1a). Patients were thoroughly informed about the nonsurgical periodontal treatment, gingivectomy, and gingivoplasty procedures, as well as the postoperative use of topical medications (chlorhexidine, saline, and hypochlorous acid). Informed consent forms were obtained from patients in all groups. All patients received nonsurgical periodontal treatment. Gingivectomy was performed on 24 patients who provided adequate oral hygiene. Patients requiring gingivectomy on the anterior 6 teeth of the maxillar or mandibular were included in the study. The gingivectomy and gingivoplasty procedures were performed by a single experienced periodontal surgeon (Sema Nur Sevinç Gül) following a standardized protocol. The patients were called for a check-up after 1st, 3rd and 7th days.

Randomization of the study groups was done using a computer as follows:

1. Hypochlorous acid (HA) group (n=8): Postoperative hypochlorous solution, 15 ml, 2 times*7 days (Crystalin®, Natural Health Products, İzmir, Türkiye)

2. CHX group (n=8): Postoperative CHX solution, 15 ml, 2 times*7 days (Kloroben®, Drogsan, Ankara, Türkiye)

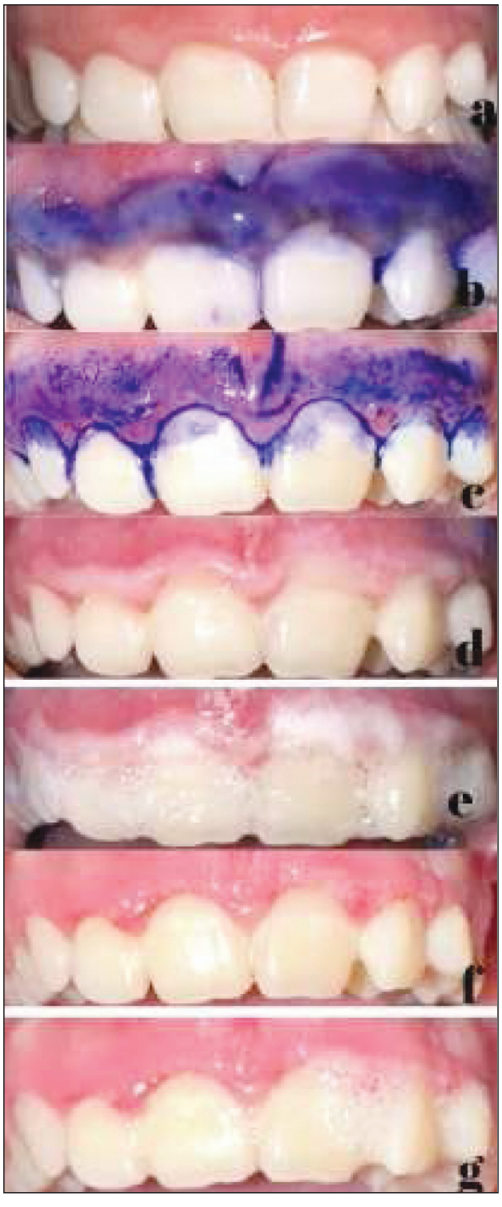

FIGURE 1: a: Before gingivectomy operation, **b:** Detection of epithelialization with plaque staining agent, post-operation 1st day, **c:** Detection of epithelialization with plaque staining agent, postoperation 7th day, **d:** Postoperation 3rd day, **e:** Detection of epithelialization with H_2O_2, post-operation 3rd day, **f:** Post-operation 7th day, **g:** Detection of epithelialization with H_2O_2, post-operation 7th day

3. Physiological saline (control) group (n=8): Postoperative 0.9% physiological saline, 15 ml, 2 times*7 days (Polifleks, Polifarma, İstanbul, Türkiye)

Inclusion Criteria

1. Systemically healthy nonsmokers

2. Grade 2 or 3 gingival overgrowth affecting at least 6 teeth symmetrically in the mandibular or maxillary anterior area

3. No attachment and bone loss

4. ≤Miller class I mobility of teeth in the operated area

5. Before the operation is planned (7 days before the surgery), the patient must ensure adequate oral hygiene to reach a full-mouth plaque index (PI) <25% and a full-mouth gingival bleeding on probing (BOP) <25%.

6. Nonsurgical periodontal treatment should be completed ≥4 weeks before surgical procedure

7. Periodontal pseudopockets ≥5 mm in at least 2 teeth

8. In the surgical site, the keratinized tissues surrounding the teeth are at least 2 mm wide.

Exclusion Criteria

1. There is a systemic disease that may affect the outcome of the treatment

2. Smoking or alcohol use

3. Patients who have undergone systemic antimicrobial therapy and surgical procedures within the last 3 months

4. Using nonsteroidal or steroidal antiinflammatory medications during the previous 15 days

5. Immunodeficiency or immunosuppressive drug therapy

6. Hereditary gingival fibromatosis

7. Pregnancy and/or breastfeeding.

8. Presence of orthodontic brackets, fixed partial dentures, removable dentures, or missing teeth in the relevant areas

9. Acute or untreated periodontitis

10. Patients who do not come for check-ups

GINGIVECTOMY AND GINGIVOPLASTY OPERATION

Infiltrative anesthesia was applied, incision lines were determined with the help of a pocket marker press, and bleeding foci were created. An external bevel incision was made with a Kirkland knife or scalpels numbered 11-12 at a 45-degree angle, 1 mm apical to the marked areas. After the incision line on the vestibular, lingual, or palatal surfaces of the tooth was

completed, the gums in the interdental area were incised with Orban blades. The remaining gingival pieces will be removed using periodontal curettes and microsurgical scissors, to correct asymmetrical and unaesthetic gingival topography.

The measured clinical periodontal parameters are as follows;

- PI[16]
- Gingival index (GI)[17]
- Bleeding on probing (BOP)
- Pocket depth
- Clinical attachment level

These clinical parameter measurements were taken from the patients before gingivectomy and again on the 7th day after gingivectomy for periodontal evaluation.

CLINICALLY WOUND HEALING PARAMETERS

Postoperative wound healing was done using some parameters. These are as follows;

Detection of Epithelialization with Plaque Staining Agent

The wound surface epithelialization was observed at baseline and on postoperative days 1st, 3rd and 7th using a plaque staining agent. Each patient had standardized photos taken of their gingiva, where wound healing was still occurring and epithelialization had not yet finished, assessing the darkly stained areas. During the photo session, a Williams periodontal probe measuring 10 mm was used to scale the image. Calculating wound surface epithelialization involved using the Image J software program (Image J 1.48V, National Institute of Health) to take pictures (Figure 1b, Figure 1c).

Detection of Epithelialization with H_2O_2

A 2nd assessment of the wound surface's postoperative epithelialization involved syringing 3% hydrogen peroxide (H_2O_2) over the surgical site. If foaming with oxygen generation is seen following the breakdown of H_2O_2 into water and oxygen by the catalase enzyme released by the blood cells in the wound region, epithelialization is deemed incomplete; if foaming is absent, it is deemed complete. The H_2O_2 test was performed on postoperative days 3 and 7 (Figure 1d, Figure 1e, Figure 1f, Figure 1g).

HISTOLOGICAL ANALYSIS

Histological examination was performed using the exfoliative cytology technique to evaluate epithelial keratinization, regeneration and/or degeneration during the healing process and to obtain epithelial samples repeatedly. On the 1st, 3rd and 7th days after gingivectomy, swab samples were taken after being placed on the edge of the wound with gentle pressure and with a sterile disposable applicator to collect epithelial material. Immediately after it was applied to the slide, it was fixed in 96% ethyl alcohol solution. Samples taken into slide storage containers were sent to the laboratory for histological examination. The obtained swab samples were stained using the Papanicolaou technique (Pap) (Figure 2).

PAPANICOLAOU TECHNIQUE

Fixed samples were subjected to washing. Then, after staining in hematoxylin solution for 3 minutes, it was washed in water. After washing, it was kept in 96% ethyl alcohol for 10 seconds. Afterwards, it was kept in Og-6 solution for 1.5 minutes. After staining,

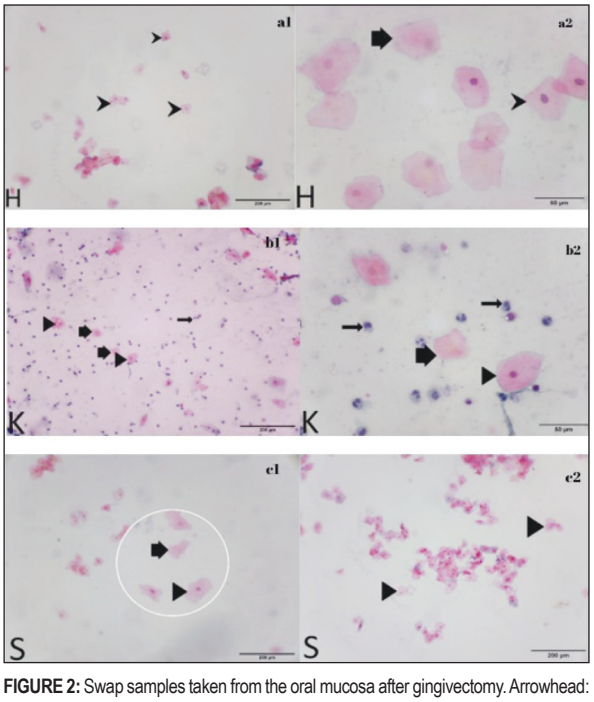

FIGURE 2: Swap samples taken from the oral mucosa after gingivectomy. Arrowhead: nucleated epithelial cell, thick arrow: nucleated epithelial cell, long arrow: neutrophil infiltration (polymorphonuclear leukocyte increase). Papanicolaou stain (x100).
H: Hypochlorous group, K: Clorhexidine group, S: Saline group

it was kept in 96% ethyl alcohol for 10 seconds. Then, it was stained in EA50 solution (Histomed, Ankara, Turkey) for 2.5 minutes. Afterwards, it was kept in 96% ethyl alcohol for 10 seconds and in 100% ethyl alcohol for 1 minute. Finally, it was kept in xylene for 2 minutes and covered with entellan. After Pap staining, the stained samples were counted under the microscope at 40x magnification, with nucleated and nonnucleated epithelial cells totaling 200 cells.

Parameters recorded for exfoliative cytological analysis: keratinization index=nucleated cells/total number of cells examined (n=200) ×100.[18]

DETERMINATION OF POSTOPERATIVE PAIN WITH VISUAL ANALOG SCALE

Visual analog scale (VAS) scores were taken on the 3rd and 7th days without any intervention to the patient. Each patient was asked to mark the pain he/she felt at that moment on this scale on the 3rd and 7th days after the operation (Figure 1). The distance from the point marked by the patient to the point where there was no pain was measured in millimeters, and the pain level the patient felt at that moment was numerically determined. Patients were prescribed analgesics containing paracetamol (Parol 500 mg, Atabay, İstanbul, Türkiye) for pain relief and were instructed to use them only when necessary (to minimize the effect of analgesics on VAS scores).

POSTOPERATIVE CARE PROTOCOL

For the first 7 days postoperatively, participants were instructed to rinse twice daily with 15 ml of the designated solution for 1 minute. During this period, no mechanical plaque control was performed on the operated areas to isolate the effect of the mouthwashes on wound healing and plaque accumulation.

STATISTICAL ANALYZE

All data were evaluated with SPSS 21.0 (SPSS Inc., Chicago, IL). One-way analysis of variance test was used, and "post hoc" Duncan Least Significant Difference (LSD) analysis was performed for intergroup comparisons, in the statistical analysis method. $p<0.05$ was considered statistically significant.

RESULTS

As a result of the analysis of the data obtained, the HA and CHX groups were statistically significantly lower than the control group in the clinical data only in the PI and BOP values measured on the 7th postoperative day ($p<0.05$). No statistically significant difference was found between the groups in other periodontal parameters ($p>0.05$). There was no statistically significant difference between groups in VAS and H_2O_2 test ($p>0.05$) (Table 1).

In the detection of epithelialization with plaque staining agent test, no statistically significant difference was found between the 1st, 3rd and 7th days in all groups. Additionally, no statistically significant difference was found between the groups (Table 2).

In the histological analysis, statistically significantly more keratinocyte cells were found in the HA group than both groups in the samples taken on day 1 ($p<0.001$). In the 3rd day samples, statistically more keratinocyte cells were found in the HA group than both groups ($p<0.05$). In the 7th day samples, statistically more keratinocyte cells were found in the HA group than in the CHX group ($p<0.05$). Statistically significantly more keratinocyte cells were found in the HA group than in the control group ($p<0.001$) (Table 3).

TABLE 1: Analysis results of clinical data (clinical periodontal parameters, VAS, H_2O_2 test)

(X̄±SD)	HA	CHX	Control	p value
PI-B	0.54±0.80	0.54±0.39	0.90±0.16	0.147
PI-A	0.68±0.74	0.55±0.21	1.06±0.20	0.026*
GI-B	1.25±0.50	1.33±0.58	1.67±0.58	0.609
GI-A	1.57±0.49	1.60±0.36	1.90±0.26	0.552
BOP-B	0.54±0.19	0.44±0.19	0.79±0.18	0.124
BOP-A	0.80±0.20	0.63±0.12	1.13±0.11	0.020**
PD-B	4.18±0.46	4.16±0.33	4.44±0.56	0.710
PD-A	2.14±0.17	2.40±0.26	2.52±1.55	0.091
VAS-3rd day	3.00±1.82	3.33±2.08	4.00±1.00	0.754
VAS-7th day	2.00±1.63	1.33±1.15	1.00±1.00	0.623
H_2O_2-3rd day	1.0±0.0	1.0±0.0	1.0±0.0	-
H_2O_2-7th day	0.5±0.58	1.0±0.0	0.66±0.58	0.445

SD: Standard deviation; HA: Hypochlorous acid; CHX: Chlorhexidine; B: Before; A: After; PI: Plaque index; GI: Gingival index; BOP: Bleeding on probing; PD: Pocket depth; VAS: Visual analogue scale; H_2O_2: Hydrogen peroxide

*There is a statistically significant difference in PI values in HA and CHX groups compared to control group on the 7th day. $p<0.05$

**There is a statistically significant difference in BOP values in HA and CHX groups compared to control group on the 7th day. $p<0.05$

TABLE 2: Evaluation of surface area staining levels between groups

(X̄±SD)	HA	CHX	Control	p value
1st day	90.30±30.71	73.60±23.52	88.93±30.12	0.737
3rd day	92.04±20.32	101.56±12.30	102.82±47.74	0.898
7th day	92.75±29.99	113.74±39.33	77.42±23.48	0.312
p value	0.993	0.263	0.636	
1st-3rd day	0.941	0.282	0.631	0.139
1st-7th day	0.911	0.117	0.670	0.510
3rd-7th day	0.974	0.604	0.359	0.372

HA: Hypochlorous acid; CHX: Chlorhexidine

TABLE 3: Results of keratinocyte amounts obtained as a result of histological analysis

(X̄±SD)	HA	CHX	Control	p value
1st day	21.5±0.91*	8.0±4.08	9.3±1.25	0.000
3rd day	29.86±4.38**	14.0±8.68	10.0±1.0	0.005
7th day	35.14±4.0***	27.31±1.75	14.17±1.04	0.000

HA: Hypochlorous acid; CHX: Chlorhexidine

* In the 1st day samples, there were statistically significantly more keratinocyte cells in the HA group than in both groups. p<0.001

**In the 3rd day samples, there were statistically significantly more keratinocyte cells in the HA group than in both groups. p<0.05

***In the 7th day samples, there were statistically significantly more keratinocyte cells in the HA group than in the CHX group. p<0.05 In the HA group, there were statistically significantly more keratinocyte cells than in the control group. p<0.001

DISCUSSION

This study investigated the effectiveness of HA on wound healing after gingivectomy. A statistically significant decrease in PI and BOP parameters was observed in the HA group. Additionally, histological examination revealed that the number of keratinocytes was significantly higher in this group compared to the others.

It has been reported that wound healing after gingivectomy occurs secondarily and that these wounds are at risk of bacterial contamination.[19] Many antimicrobial agents have been used for this purpose, with CHX being recognized as the gold standard to date due to its antiplaque and antibacterial properties. However, in clinical studies, this agent has been shown to have desquamation in the epithelium, loss of taste, discoloration of the tongue and teeth, and cytotoxic effects on gingival fibroblast cells in *in vitro* studies.[20,21] Therefore, chemotherapeutic agents with minimal side effects are needed to accelerate wound healing.

CHX is the most commonly used mouthwash. Although cetylpyridinium chloride, H_2 Ocean Sea Salt, *Commiphora molmol* 0.5%, CHX 0.12%, and essential oils reported better healing than the negative control, there are no studies on HA for wound healing after periodontal surgery.[11,22-25] HA was used as an antimicrobial solution for treating inflamed wounds during the 1st World War.[26] The immune system metabolism also synthesizes this organic substance during the phagocytosis of antigens.[27] Besides having a broad antimicrobial spectrum for inhibiting numerous Gram-positive and Gram-negative microorganisms, HA also has significant antiinflammatory and proliferative activity.[28-30] Stabilized HA encourages re-epithelialization and regulates the bacterial bioburden in human acute wounds, which are standardized.[13,31]

As a result of histological analysis, statistically significantly more keratinocytes were observed in the HA group than in the other groups. Consistent with our study, in a study conducted in the field of dermatology, the effectiveness of HA on wound healing was investigated by comparing it with physiological Saline, and statistically significantly more keratinocytes were found.[31] In another study, the application of HA and physiological saline on the wound was compared microbiologically and histologically, it was observed that the epithelial thickness was thicker in wound healing in the HA applied group.[32] Robson et al. found that topical HA (0.01%) treatment for 30 minutes enhanced wound healing and reduced bacterial load in both infected and non-infected wounds in rats.[33] Plata et al. demonstrated that HA was comparable to CHX in reducing the PI. Both groups showed a similar reduction in the recolonization of *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Eubacterium nodatum*. Additionally, the HA protocol was found to be noninferior to the CHX protocol in managing *Treponema denticola* and *Aggregatibacter actinomycetemcomitans*. HA enhanced periodontal healing and effectively reduced the recolonization of periodontopathic bacteria during the postoperative period.[34]

Although the results of our histological study were superior in the HA group, no statistically significant difference was found between the groups in the results we obtained with the VAS, H_2O_2 foaming test and staining test. In the study conducted by Alpan on palatal donor site healing, it was reported that the hypochlorous group had lower VAS scores, similar to the Flurbiprofen group.[35] This result does not support our results, which may be attributed to the limited sample size in our study.

Furthermore, the reason for the result of the H_2O_2 foaming test and staining test was that the data obtained in the early period (day 7) were based on visual evaluation, and no visible differences were observed. However, histological analysis revealed a statistically significant difference in the quantity of keratinocytes, even during the early wound-healing phase. As there are no similar studies available, a direct comparison could not be made. This study is the first to examine the contribution of HA to early wound healing after gingivectomy.

Our study's limitations include an insufficient sample size. Since this study was designed as a pilot study, further research with a larger sample size is needed. Additionally, extending the follow-up period to 1-3 months could allow for the evaluation of the later stages of wound healing.

CONCLUSION

HA appears to be a promising wound antiseptic agent based on these findings. HA can be preferred as an effective alternative to eliminate the disadvantages of CHX, which is frequently prescribed for wound care after periodontal surgery. Further studies are needed to evaluate long-term results.

Source of Finance

This research was supported by TÜBİTAK 2209-A project.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Sema Nur Sevinç Gül;* ***Design:*** *Alparslan Dilsiz;* ***Control/Supervision:*** *Sema Nur Sevinç Gül;* ***Data Collection and/or Processing:*** *Bahtiyar Zana Güzel, Dilruba Rana Çögenli;* ***Analysis and/or Interpretation:*** *Merve Pekince Özöner, Sema Nur Sevinç Gül;* ***Literature Review:*** *Sema Nur Sevinç Gül, Dilruba Rana Çögenli;* ***Writing the Article:*** *Sema Nur Sevinç Gül, Alparslan Dilsiz;* ***Critical Review:*** *Sema Nur Sevinç Gül, Alparslan Dilsiz;* ***References and Fundings:*** *TÜBİTAK;* ***Materials:*** *Bahtiyar Zana Güzel.*

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