ORIGINAL ARTICLE

DOI: https://doi.org/10.20453/reh.v34i2.5531

Cite as:
Artieda CD, Paltas ME, Andrade AL. Comparison of hyaluronic acid and bee honey on healing and bacterial growth in guinea pig mucosa: *in vivo* study. Rev Estomatol Herediana. 2024; 34(2): 121-128. DOI: 10.20453/reh.v34i2.5531

Received: August 16, 2023
Accepted: April 22, 2024
Online: June 29, 2024

Conflict of interests: The authors declare that they have no conflict of interest.
Funding: Self-funded.
Ethics approval: Work approved on November 26, 2019 by the Ethics Committee of Universidad Central del Ecuador, with code 019-FO-PG-2019.
Authorship Contribution: All authors contributed to the preparation of this manuscript.
Acknowledgments: Our appreciation to Universidad Central del Ecuador, to the Facultad de Odontología and to the Centro de Biología, especially to Dr. Javier Tingo, veterinarian at the Centro de Biología of the Universidad Central del Ecuador.

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Comparison of hyaluronic acid and bee honey on healing and bacterial growth in guinea pig mucosa: *in vivo* study

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ABSTRACT

Objective: To compare *in vivo* the topical application of hyaluronic acid and bee honey on healing and bacterial growth in the mucosa of guinea pigs. **Materials and methods**: *In vivo* study, applied to a sample of 30 guinea pigs, classified in three groups (A, B and C), all with the same conditions (place, feeding and temperature). During five consecutive days, both in the morning and in the afternoon, the following treatments were applied topically: Hyaluronic acid in group A, bee honey in group B, and in group C (control group) no substances were applied. This was carried out using a hypodermic syringe. After sedation, a 4-mm circular incision was made in the guinea pig mucosa in the left infero-lateral region of the incisors. The following characteristics were identified at the wound site: bleeding, edema, erythema (4, 6 and 8 days), scar tissue and presence of suppuration (8 days), and bacterial culture (to measure colony forming units [CFU]). **Results:** The group to which hyaluronic acid was applied in the evolution of the wound showed a decrease in bleeding, edema and erythema; in addition, the formation of scar tissue of 4 mm on the sixth day was 60.00% (n = 6), there was epithelial union of 80.00% (n = 8) on the eighth day and showed lower CFU in the analysis ranges. **Conclusion:** Topical application of hyaluronic acid contributes to scar tissue formation, wound closure and decreased bacterial formation.

Keywords: healing; hyaluronic acid; honey; edema; erythema; suppuration.

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INTRODUCTION

Hyaluronic acid (HA) is a chemical substance in the vitreous gelatin of cow`s eyes. It is considered a high molecular weight polysaccharide, which is found in the extracellular matrix of connective tissue, synovial fluid, and it is present in high concentrations in the periodontium, gingiva and periodontal ligament (1, 2). In the field of dentistry, HA has shown antibacterial and anti-inflammatory effects during the healing process of periodontal lesions (1).

Different studies have proven the bacteriostatic action of HA. In the literature review conducted by Dahiya and Kamal (1), the study by Pirnazar et al. is mentioned, whose objective was to determine whether, depending on the concentration or molecular weight of HA, it had bactericidal or bacteriostatic effects on the growth of certain oral and non-oral strains in different species, namely: *S. mutans*, *P. gingivalis*, *Prevotella oris*, *Actinobacillus actinomycetemcomitans*, *S. aureus* and *Propionibacterium acnes*. In their results they mention that there was no bactericidal effect on any strain, regardless of the concentration or molecular weight of the HA used; however, there were notable bacteriostatic effects on growth in some of them, with a different pattern according to each strain. They mention that on *S. mutans* and *P. gingivalis* the effect was minor, while, regardless of HA concentration or molecular weight, *S. aureus* and *A. actinomycetemcomitas* showed more significant bacteriostatic effects. This could indicate that the use of HA during surgical interventions may reduce the risk of infection due to a decrease in bacterial contamination. The defense mechanism can be attributed to special characteristics, such as being viscoelastic and hygroscopic; these properties modify the environment and thus increase the consistency of the active component and serve as a barrier to prevent the passage of bacteria into tissues, including periodontal tissue (1, 2).

On the other hand, the first evidence of honey consumption dates back to the Mesolithic period (6000 years B. C.), while its use as a medicine began to be applied by the Mesopotamians 2500 B. C.; in addition, the ancient Egyptians, Greeks, Romans, among others, used honey to heal wounds (3, 4). Bee honey can be defined as a sweet-tasting, unfermented substance made by bees that has been used since ancient times, either as a food and/or medicinal product (3). Hippocrates, in his work Considerations on the treatment of wounds, mentions that honey can be used for healing (3-5). Bee honey was rediscovered in the Modern Age as an alternative antibacterial treatment against microorganisms present in wounds that are resistant to antibiotics (3-6). This is why many studies aim to demonstrate the properties of honey that help in the repair of wounds of various etiologies (4); in addition, it is considered a natural alternative treatment that reduces the cost of modern treatments, and it is easily accessible (3).

The mechanism of action occurs due to the antioxidants in honey, which scavenge free radicals as a product of the inflammatory stage, reduce oxidative stress and, in turn, the inflammatory process. At the same time, honey decreases the levels of prostaglandins, which is a substance that favors inflammation. Additionally, by eliminating bacteria that could stimulate the inflammatory response, it reduces this reaction (3, 4). The healing effect of honey may be the result of a combination of factors, such as the formation of an environment with humid characteristics to favor cellular increase, the elimination of devitalized tissue with necrotic areas, the reduction of edema, the formation of granulation tissue and its consequent epithelization, and antibacterial and fungicidal properties. In addition, its acidity increases blood oxygenation, which helps to repair tissues (3, 4).

Bee honey has antibacterial properties due to the presence of some substances such as natural acidity, phenolic compounds and hydrogen peroxide. These components help inhibit the growth of bacteria, which contributes to its ability to fight infection and promote wound healing. Bee honey has traditionally been used for medicinal purposes due to its antibacterial properties (3, 4).

The guinea pig, also known as *conejillo de Indias* or *cuy*, native to South America, shares some similar characteristics with the human gum, and being extremely docile, it is ideal for laboratory animals (7, 8).

The aim of this *in vivo* study was to compare the topical application of HA and honey on healing and bacterial growth in guinea pig mucosa.

MATERIALS AND METHODS

This investigation is an *in vivo*, single-blind, comparative and longitudinal study. The data from the experimental work were analyzed in the statistical package IBM® SPSS v. 25. A descriptive statistical analysis was performed using the software. The Kolmogorov-Smirnov normality test was applied to determine whether the variables are parametric or nonparametric. The chi-square test and ANOVA for independent samples were applied, at a significance

level of less than 0.05, which demonstrates statistical significance in relation to the substances used and clinical characteristics of the wound.

The sample was selected based on the 3Rs of animal experimentation (replace, reduce and refine). The sample consisted of 30 guinea pigs, all in the same conditions (place, feeding and temperature), with physiological similarities in terms of the formation and constitution of the buccal mucosa. Study groups of 10 guinea pigs each were formed: two groups for the application of substances (A: hyaluronic acid; B: bee honey) and a control group (C: physiological healing), considering the inclusion criteria (healthy males of the same genetic line and type, weighing 900-1,000 g, 3 to 4 months of age, with balanced feeding). Sick or injured guinea pigs were excluded.

The guinea pigs were acquired at the biotherium of the Universidad Central del Ecuador. Apart from that, they were evaluated by the veterinarian in charge of the Biology Center to identify the presence or absence of diseases and to select them according to the inclusion criteria.

Regarding the substances, the HA (Revanesse Pure®) was purchased from Medsurgical Ecuador, an authorized distribution center. Manufacturer: Prollenium Medical Technologies Inc. is a substance manufactured according to a complete series of tests in accordance with ISO 10993, lot: 18J042-15-1. Presentation: 14 mg/mL with 1 mL syringe with 30G needle, a non-cross-linked substance. Date of issue: August-2019; date of expiration: August-2020.

Honey (*Apis mellifera*) was purchased from Camari (Agricultural and Artisanal Center), accredited by the Ecuadorian Quality Management System ISO 9001-2018. Manufacturer: Pacha beekeeping association, lot: 06052019. Presentation: pure bee honey of 500 g, which complies with the Ecuadorian Technical Standard NTE INEN 1572. The bee honey used in the study complies with physical, chemical and microbiological requirements that ensure to a microbiological and food analysis carried out at the Faculty of Chemical Sciences of Universidad Central del Ecuador. It is a viscous substance. Date of issue: June-2019; expiration date: June-2020.

The adaptation phase began with a gradual change of feeding for 10 days. On day 11 of the stay in the biotherium, the veterinarian verified the conditions and weight of the guinea pigs. To determine the anesthetic dose, parenteral intramuscular ketamine was used for conscious sedation with a 1 cc syringe at a dose of 0.1 mg/kg body weight, plus atropine sulfate at a dose of 0.04 mg/kg body weight (Ket-A-Xyl®). Then, topical anesthesia (lidocaine 10% spray) was applied, and a 4-mm circular incision was made in the mandibular region on the left side lateral to the teeth with circular scalpel no. 4, posterior to the incision. Right after that, a drop of HA was applied, using a 1 cc syringe with a 30G needle, in group A (Figure 1A), while in group B bee honey was administered by means of a 10 mL syringe with the needle cut at the pivot level (Figure 1B). Group C, which served as the control group, did not receive any substance. After the procedure, the guinea pigs were placed in thermal blankets inside cages, with appropriate temperature for their recovery.

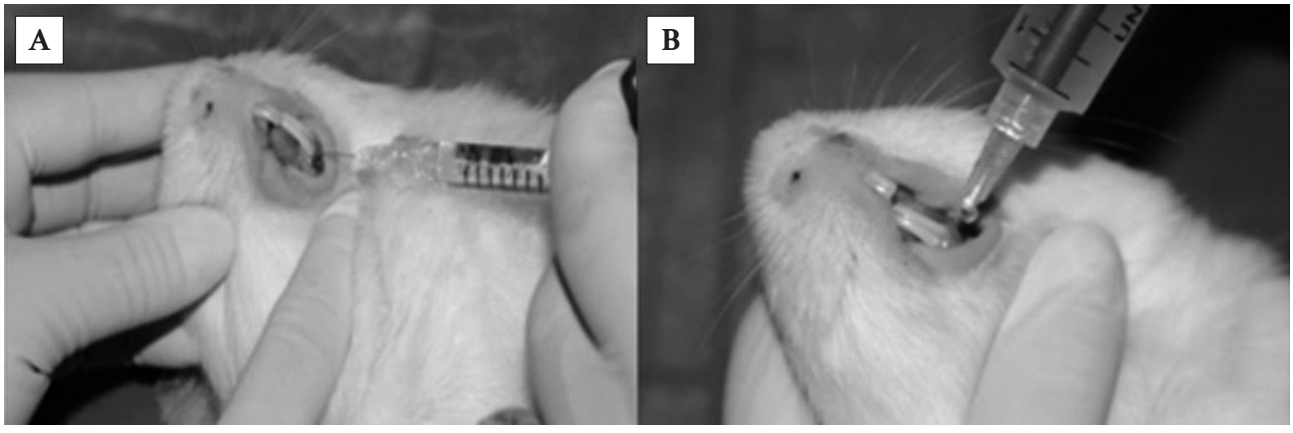

Figure 1. Immediate topical application of hyaluronic acid (A) and honey (B).

On the fourth and sixth day after incision, clinical examination of the wound was performed in the three groups to evaluate its characteristics: bleeding, edema and erythema. In addition, the amount of existing scar tissue was assessed using a Williams periodontal probe (Figure 2). For the evaluation of the scar tissue size, measurements

were taken from 0 to 4 mm. A mathematical calculation was performed considering that 4 mm is 100.00% of the healed surface. Therefore, among the results of the measurement are reference percentage values: 4 mm = 100.00%; 3 mm = 75.00%; 2 mm = 50.00%; 1 mm = 25.00%; 0 mm = 0.00% of healed surface.

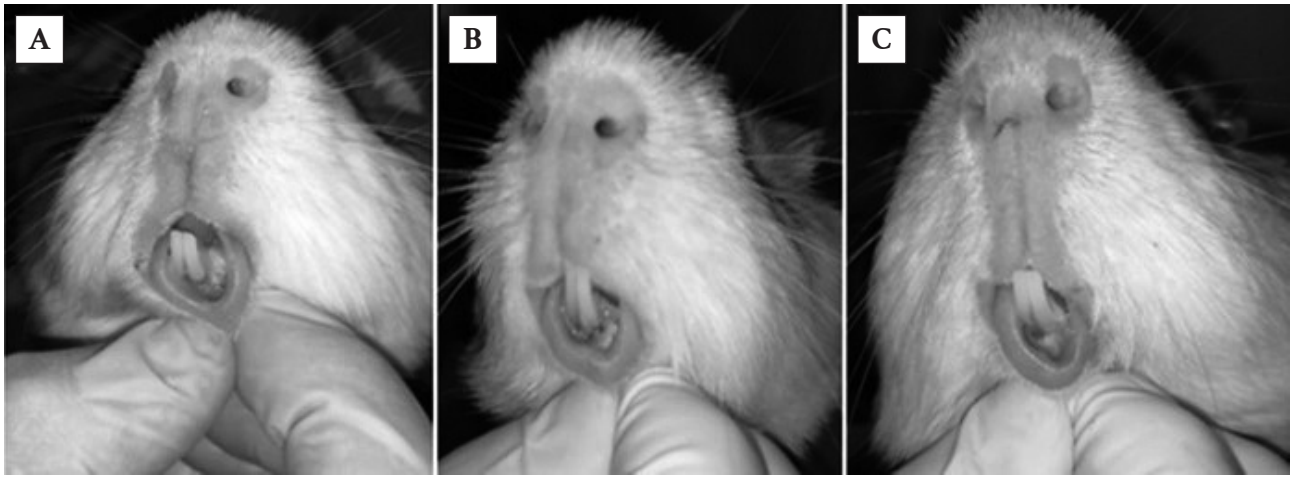

Figure 2. Wound characteristics on the fourth day. A) Hyaluronic acid; B) Bee honey; C) Control group.

On the fifth day after the incision, the wound was swabbed for bacterial culture in the three study groups. 24 hours after seeding, the Petri dishes were removed from the incubator to count the colony forming units (CFU) of the three study groups (Figure 3). On the eighth day after incision, clinical examination of the wound was performed in all three groups to evaluate wound characteristics: bleeding, edema, erythema, suppuration and epithelial junction.

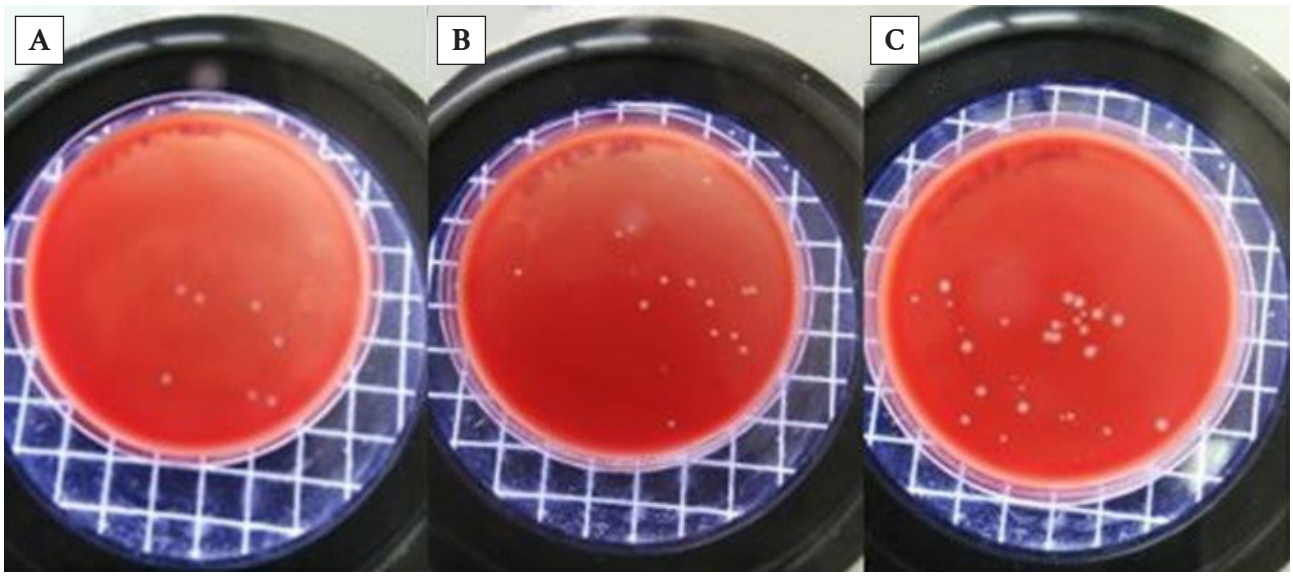

Figure 3. CFU count of two Petri dishes for each sample of hyaluronic acid group (A), honey bee group (B) and control group (C).

Dichotomous data were used for the quantification of the dependent variables of the study, which correspond to the wound characteristics mentioned previously, by observation and palpation. They were categorized according to the absence or presence of the clinical feature.

This research had the approval of the Ethics Committee of the Universidad Central del Ecuador, on November 26, 2019.

RESULTS

The total sample included in the study was 30 guinea pigs, divided into three groups of 10 (33.33%; n = 10): A (hyaluronic acid [HA]); B (bee honey); C (control group). All guinea pigs were kept in the same conditions and mucosal substances were applied to compare healing and bacterial growth.

On the fourth day, group A (HA) presented bleeding in 16.67% (n = 5) of the cases; group B (bee honey) in 23.33% (n = 7); and group C (control group) in 23.33% (n = 7). Both erythema and edema were present in 100.00% (n = 30) of cases in all three groups.

On the sixth day, group A (HA) showed bleeding in 13.33% (n = 4) of the cases; group B (bee honey) in 16.67% (n = 5); while in group C (control group) it occurred in 23.33% (n = 7). As for erythema, group A (HA) evidenced it in 13.33% (n = 4) of the cases, group B (bee honey) in 16.67% (n = 5), and group C (control group) in 23.33% (n = 7). Regarding edema, group A (HA) presented it in 3.33% (n = 1) of the cases, group B (bee honey) in 10.00% (n = 3), and group C (control group) in 16.67% (n = 5).

On the eighth day, group A (HA) presented bleeding in 6.67% (n = 2), group B (bee honey) in 10.00% (n = 3), and group C (control group) in 20.00% (n = 6). Regarding erythema, group A (HA) showed it in 10.00% (n = 3), group B (bee honey) in 13.33% (n = 4), and group C (control group) in 16.67% (n = 5). Regarding edema, group A (HA) presented it in 3.33% (n = 1), group B (bee honey) in 6.67% (n = 2), and group C (control group) in 10.00% (n = 3). The data indicate that HA contributes to a decrease in clinical wound characteristics compared to the use of bee honey and physiological healing (Table 1).

Table 1. Comparison and evaluation of the clinical characteristics of the wound between days 4-8 (day 6: measurement of scar tissue; day 8: presence of purulent discharge and epithelial junction).

Clinical features	Substances												Total	
	Hyaluronic acid (A)				Bee honey (B)				Control group (C)					
	Yes		No		Yes		No		Yes		No			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Bleeding														
Day 4	5	16.67	5	16.67	7	23.33	3	10.00	7	23.33	3	10.00	30	100.00
Day 6	4	13.33	6	20.00	5	16.67	5	16.67	7	23.33	3	10.00	30	100.00
Day 8	2	6.67	8	26.67	3	10.00	7	23.33	6	20.00	4	13.33	30	100.00
Erythema														
Day 4	10	33.33	0	0.00	10	33.33	0	0.00	10	33.33	0	0.00	30	100.00
Day 6	4	13.33	6	20.00	5	16.67	5	16.67	7	23.33	3	10.00	30	100.00
Day 8	3	10.00	7	23.33	4	13.33	6	20.00	5	16.67	5	16.67	30	100.00
Edema														
Day 4	10	33.33	0	0.00	10	33.33	0	0.00	10	33.33	0	0.00	30	100.00
Day 6	1	3.33	9	30.00	3	10.00	7	23.33	5	16.67	5	16.67	30	100.00
Day 8	1	3.33	9	30.00	2	6.67	8	26.67	3	10.00	7	23.33	30	100.00
Total	40		50		49		41		60		30		270	
													Chi-square p-value	
Purulent discharge on day 8	0	0.00	10	33.33	1	3.33	9	30.00	0	0.00	10	33.33	1	0.355
Epithelial junction on day 8	8	26.67	2	6.67	6	20.00	4	13.33	3	10.00	7	23.33	17	0.034
Total	8	2.00	12	18.00	7	5.00	13	15.00	3	7.00	17	13.00		

Table 1. (*Continuation*).

	Measurement	Occupied area (%)	Hyaluronic acid		Bee honey		Control group		Total	
			n	%	n	%	n	%	n	%
Scar tissue in day 6	0 mm	0.00	0	0.00	0	0.00	1	3.33	1	3.33
	1 mm	25.00	0	0.00	0	0.00	0	0.00	0	0.00
	2 mm	50.00	0	0.00	0	0.00	4	13.33	4	13.33
	3 mm	75.00	4	13.33	5	16.67	4	13.33	13	43.33
	4 mm	100.00	6	20.00	5	16.67	1	3.33	12	40.00
Total			10	33.33	10	33.33	10	33.33	30	100.00

In the evaluation of the scar tissue on the sixth day, it was found that 43.30% (n = 13) presented a measurement of 3 mm, equivalent to 75% of the wound covered, being predominant in group B (bee honey) with 16.67% (n = 5). Scar tissue of 4 mm, equivalent to 100.00% of the covered wound, was also observed in 40.00% (n = 12), being predominant in group A (HA) with 20.00% (n = 6). Meanwhile, group C (control group) obtained measurements ranging from 0 to 3 mm (Table 1). Therefore, topical application of HA promotes the formation of scar tissue in the wound compared to the use of honey and physiological healing.

On the eighth day, during wound evaluation, suppuration was evident in group B (bee honey) in 3.33% (n = 1) of the total sample. In relation to the epithelial junction, in group A (HA) a closed wound was observed in 27.67% (n = 8); in group B (bee honey) in 20.00% (n = 6); and in group C (control group) in 10.00% (n = 3). A p-value of 0.034 was obtained, indicating a significant association between the substances administered and epithelial junction (Table 1). Therefore, topical application of HA contributes to wound closure compared to the use of honey and physiological healing.

When the CFU count was performed for each guinea pig, it was observed that, in the range of 0.00-30.00 CFU, group A (HA) presented 26.60% (n = 8); group B (bee honey), 6.60% (n = 2); and group C (control group), 0.30% (n = 1). In the range of 30.01-60.00 CFU, group A (HA) presented 6.60% (n = 2); group B (bee honey), 19.68% (n = 6); and group C (control group), 13.32% (n = 4). In the range of 60.01-100.00 CFU, group A (HA) presented 0.00% (n = 0); group B (bee honey), 6.60% (n = 2); and group C (control group), 13.32% (n = 4). In the range of 100.01-200.00 CFU, group A (HA) presented 0.00% (n = 0); group B (bee honey), 0.00% (n = 0); and group C (control group), 6.70% (n = 1) (Table 2). The topical application of HA contributes to the decrease of CFU, presenting a lower quantity in the wound compared to the use of honey and physiological healing.

Table 2. Colony forming unit (CFU) count.

Groups/study	Colony forming units (CFU)								Total	
	0-30		30.01-60		60.01-100		100.01-200			
	n	%	n	%	n	%	n	%	n	%
Hyaluronic acid	8	26.60	2	6.60	0	0.00	0	0.00	10	33.30
Bee honey	2	6.60	6	19.98	2	6.60	0	0.00	10	33.30
Control group	1	0.30	4	13.32	4	13.32	1	6.70	10	33.30
Total	11	36.6	12	40.00	6	20	1	3.33	30	100.00

DISCUSSION

HA, being a component found in high percentage in the extracellular matrix, has the characteristic of attracting water in large quantities to the intercellular space, thus achieving a tight and gelatinous cellular junction (9). It is a substance produced by fibroblasts that can be administered exogenously, enhancing the formation of matrix and elastic fibers, contributing to collagen synthesis. Several authors have reported important properties of HA, such as angiogenesis, remodeling and tissue maintenance (1, 9-11).

Topical administration of HA has proven usefulness as adjuvant therapy in gingivitis, chronic periodontitis, oral ulcers, and in wounds during the post-surgical period, favoring tissue recovery (12, 13). Pistorius et al. (14) evaluated the efficacy of topical HA administration for the treatment of gingivitis and identified that topical application of HA-containing preparation was a potentially useful adjunct.

In the study by Park et al. (15), a better macroscopic and microscopic tissue recovery was evidenced in experimental animals using HA: evidence of abscesses, neutrophilic infiltrate and less necrosis than in the control group. Overall, immediate local application of HA to wounds significantly reduced the occurrence and duration of surgical site infection in an animal model (15-18).

In this study, in relation to the epithelial junction (measured on the sixth day centripetally with the aid of a periodontal probe), it is evident that the group to which HA was applied shows a better response with measurements of 4 mm of scar tissue in 20.00% (n = 6) of the guinea pigs, showing a more compact scar tissue. On the eighth day of the clinical analysis, the wound is closed in 8 guinea pigs (27.67%) of the group to which HA was applied. This indicates a healing activity in relation to the control group. The group to which HA was applied presented a greater number of samples in the range of 0-30 CFU, which allows us to conclude that it has antibacterial activity in relation to the control group.

Studies suggest that honey has wound repairing effects and that it helps in the healing process, not only because of its antioxidant activity, but also because of its anti-inflammatory and inflammation regulating properties, an effect that can be evidenced during the evolution of wounds (5). Ndayisaba (18) discusses the rediscovery of the reparative properties of bee honey and conducted a study on 40 patients who had wounds with various causes, as well as burns with infection. This author found the reparative effectiveness of honey in 88% of the cases.

In this study, in relation to the group to which bee honey was administered, it was evidenced that, on the fourth day after the incision, there was the presence of bleeding in 23.33% (n = 7) of guinea pigs, besides erythema and edema in all guinea pigs 100.00% (n = 30). On the sixth day after the incision, bleeding and erythema were observed in 16.67% (n = 5) and edema in 10.00% (n = 3). On the eighth day, the presence of bleeding was 10.00% (n = 3), erythema in 13.33% (n = 4) and edema in 6.67% (n = 2). Apart from that, one (3.33%) guinea pig presented purulent discharge.

On the sixth day in the centripetal wound measurement, group A (HA) evidences a better response with measurements of 4 mm of scar tissue in 16.67% (n = 5) of guinea pigs, showing a thin granulation tissue.

On the eighth day of clinical analysis, the wound is closed in 6 guinea pigs, corresponding to 20.00% of the group to which honey was applied. This indicates that it has a healing activity in relation to the control group.

The group to which bee honey was applied presented a greater quantity of samples in the range 30.01-60 CFU, which allows us to conclude that it has antibacterial activity in relation to the control group.

During the study, we saw some limitations that are related to the difficulty in handling and sudden changes in the environment, which affect the behavior and health of the research subjects, as well as feeding, which can cause possible injuries during chewing and aggressive habits of guinea pigs.

CONCLUSION

Topical application of HA contributes to the formation of 4-mm scar tissue (day 6: 20.00%; n = 6), wound closure (day 8: 27.67%; n = 8) and decreased bacterial formation (range 0.00-30.00 CFU; 26.60%; n = 8), compared to topical use of honey bee and physiological healing. There is a statistically significant association between the substances administered and epithelial junction.

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