



## The Effect of Topically Applied Hyaluronic Acid on Skin Wound Healing in Rabbits

Ammar M. Rajab<sup>1\*</sup>; Ghada A. Taqa<sup>2</sup> and Wael T. Al-Wattar<sup>3</sup>

<sup>1</sup>Ministry Of Health, Nineveh Health Directorate, Mosul, Iraq

<sup>2</sup>Department of Dental Basic Science, College of Dentistry, University of Mosul, Mosul, Iraq.

<sup>3</sup>Department of Oral and Maxillofacial Surgery, College of Dentistry, University of Mosul , Mosul, Iraq

\*Corresponding Author: Ammar M. Rajab, E-Mail: [ammar.dep4@student.uomosul.edu.iq](mailto:ammar.dep4@student.uomosul.edu.iq)

### ABSTRACT

This study aims to evaluate the effect of the topical application of hyaluronic acid cream 0.2% in the skin wound healing in rabbits. Thirty two healthy New Zealand adult male rabbits approximately at the same age and weight were involved in this study; all animals were anaesthetized using a 40 mg/kg ketamine and xylazine 4 mg/kg injection intramuscularly. The skin of the dorsum area of each rabbit was aseptically prepared and then two incisions (1cm in length) were made on the skin. Wounds were left without suturing to heal by secondary intention healing. Each animal had two wounds (wounds divided into two groups according to the type of treatment): one treated with hyaluronic acid cream twice a day, the second wound was left untreated. The application of the cream was repeated daily. Rabbits were divided into 4 groups according to sacrifice days; every eight rabbits were sacrificed in days 1st, 3rd, 7th, and 14th days, biopsies were taken and sent for histological assessment. Group treated with hyaluronic acid showed significant improvement in wound healing capacity in the skin of rabbits; granulation tissue formation and re-epithelialization were significantly improved in the hyaluronic acid group compared with the control group in the 3rd and 7th days. Also, Re-epithelialization in the hyaluronic acid group was better on the 14th day of this study compared with the control group. Hyaluronic acid cream increases the rate of wound healing in the skin of rabbits.

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### INTRODUCTION

The skin is the biggest organ in the human body and serves as a physical, chemical, and biological barrier. It is essential for living a healthy life. (Darwin *et al.*, 2018). The skin is an important structure that protects interior organs from mechanical damage, microbial infection, UV light, and severe temperatures. (Rodrigues *et al.*, 2019). The goal of topical wound treatment is to repair the wound as quickly as possible in order to reduce infection and decrease pain, discomfort, and scarring. An effective wound treatment should lower the quantity of necrotic tissue while also preventing microbial invasion. (Mayet *et al.*, 2014).

Wound healing is one of the most complex processes, requiring the delicate synchronization of multiple distinct cell types in successive phases, including hemostasis, the inflammatory phase, the

proliferative phase, and the remodeling phase. (Wang *et al.*, 2018).

The wounded blood vessels constrict as an initial reaction to a wound. When platelets come into touch with exposed collagen and extracellular matrix, they release clotting factors to create a fibrin clot and growth factors to assist wound healing. (Clark., 2003). The fibrin clot stops blood flow and acts as a scaffold for arriving inflammatory cells; neutrophils are attracted first, followed by monocytes 48–96 hours later, which are converted into tissue-activated macrophages at the wound site. (Rodrigues *et al.*, 2019).

Angiogenesis commences once the inflammatory phase finishes, and pericytes inside the basal lamina are activated, scaffolding and providing structural stability to the endothelial cells. (Ansell and Izeta, 2015). The clot is then invaded by fibroblasts, which migrate, proliferate, and create contractile granulation tissue, setting off the proliferative phase.

Fibroblasts develop into myofibroblasts, which bring the wound borders together. (**Martin, 1997**). The dividing fibroblasts deposit a new extracellular matrix (ECM) and collagen. During the final remodeling phase, the newly laid collagen matrix becomes organized and cross-linked. Re-epithelialization takes place at the same time as unipotent epidermal stem cells proliferate from the basement membrane and terminally differentiated epidermal cells dedifferentiate. Numerous cell signaling events and cytokines are required to orchestrate these events (**Donati et al., 2017**).

Hyaluronic acid (HA) is a versatile, biocompatible, nonimmunogenic natural product (**Sudha and Rose, 2019**). It is a glycosaminoglycan-related polysaccharide comprised of a basic unit of two sugars, glucuronic acid and N-acetyl-glucosamine. HA has a large molecular mass in many human body regions, including the synovial fluid that surrounds joints, cartilage, and eye and skin tissues. (**Neuman et al., 2015**).

HA is found in humans, bovines, and roosters, as well as microbes. Commercially HA was initially isolated from *Streptococcus* bacteria spp. (*Streptococcus zooepidemicus*), followed by *Bacillus* spp., *Lactococcus lactis*, *Agrobacterium* sp., and *Escherichia coli* as hosts. HA is also found in mollusks and yeasts (*Cryptococcus neoformans*) (**Liu et al., 2011; Fallacara et al., 2018**).

Biocompatibility, biodegradability, muco-adhesivity, hygroscopicity, and viscoelasticity are some of the distinctive physicochemical features of HA. (**Fallacara et al., 2018**). HA influences cellular activity by preserving tissue integrity. It also plays many functions in repairing injured tissues and encouraging cell adhesion and differentiation during inflammation and embryonic development. (**Jiang et al., 2007**). This study aims to identify the role of topical application of HA on the acceleration of wound healing in rabbits.

## **MATERIALS AND METHODS**

### **Animals:**

The present study was performed in a total number of Thirty-two New Zealand adult male rabbits aged about 5-7 months, weighing 1.5 - 2 kg. The animals were kept in the animal's house of the college of dentistry, Mosul University, Iraq. Animals were separated in plastic cages at room temperature  $22 \pm 2$  C°, kept in 12 hours light, 12 hours dark, and free access to food and tap water.

### **Material used:**

The hyaluronic acid cream used in this study has been brought from (fidia farmaceutici s.p.a., Abano Terme, Italy) as a commercial product named

hyalu4skin cream, the main ingredient in this cream is hyaluronic acid 0.2%.

### **Surgical procedure:**

Each rabbit was given mixed 40 mg/kg ketamine (KETALROM-50, romvac company, SA) with xylazine (holland) 4 mg/kg injection intramuscularly in the thigh muscle of the rabbit (**Ahirwar et al., 2021**). The rabbit's weight is recorded using electronic digital scales; after 5-10 minutes. The rabbit reflexes were checked to ensure that anaesthesia was taken.

Animals in all groups were subjected to a septic preparation of the area of interest. Each animal was laid down in a prone position. A full-thickness 1cm longitudinal skin incision was made. Each rabbit had two incisions on the skin of the dorsum area. All the defective wounds left without suturing to heal by secondary intentional healing.

Two stab incisions were made at the dorsum area through the skin of each rabbit, the first incision treated with HA cream, the second incision left without treatment. Wounds were divided randomly into two experimental groups; each group consisted of Thirty-two wounds according to the treatment material used.

- **Group 1 (HA 0.2%):** Thirty-two Skin incisions treated with topical HA cream 0.2% two times daily.
- **Group 2 (control):** Thirty-two Skin incisions were left untreated.

Animals were subdivided into four groups according to the time of sacrifice. Eight animals have sacrificed on day 1, day 3, day 7, and day 14 after the surgical procedure. Biopsies were collected and subjected to histopathological assessment.

### **Histopathological scoring:**

Many authors like **Sultana et al., (2009); Gupta et al., (2015)** concluded histology scoring to evaluate the histopathology slide's healing status, which consists of three criteria: inflammatory cell infiltration, granulation tissue formation, and re-epithelialization parameters. (Table 1,2 and 3).

Table 1: Criteria of the inflammatory response parameter

Score 1	Nil No inflammatory cells were observed in the field of surgery (X10).
Score 2	Mild If inflammatory cells occur in low numbers, less than $\frac{1}{2}$ of the field (X10).
Score 3	Moderate Inflammatory cells might be observed in more than $\frac{1}{2}$ of the field (X10).
Score 4	Severe or abundant when inflammatory cells exist in enormous numbers, greater than $\frac{3}{4}$ of the field (X10).

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**Table 2:** Criteria for the amount of granulation tissue formation.

Score 1	Absent of granulation tissue development in the wound.
Score 2	The amount of granulation tissue development in the wound gap is minimal.
Score 3	The quantity of granulation tissue development is moderate in tissues.
Score 4	The total quantity of granulation tissue development in the wound is profound.

**Table 3:** Criteria of re-epithelialization parameters

Score 0	Re-epithelialization along the margin of the wound.
Score 1	Re-epithelialization covers less than half of the wound.
Score 2	Re-epithelialization covering more than half of the wound.
Score 3	Re-epithelialization covers the whole wound, uneven thickness.
Score 4	Re-epithelialization covers the whole wound, normal thickness.

### Statistical Analysis:

The data were expressed as mean  $\pm$  standard deviation (S.D.), the variation between two experimental sets was statistically evaluated using the Mann-Whitney U test. Statistical significance was accepted for ( $p$ -value  $\leq *0.05$ ).

## RESULTS

In the present study, all the animals involved survived until the sacrifice days (1st, 3rd, 7th, and 14 days). In each sacrifice day of study, the biopsies were collected, slides prepared and stained by hematoxylin and eosin, and sent for histologists to assess histological scores (inflammatory response, granulation tissue formation, and epithelialization scoring).

### On the first day after surgery

The inflammatory cell infiltration showed a similar result in both groups; both groups showed a moderate number of inflammatory cells in the field of operation, HA group showed a fewer amount of inflammatory cells, the mean of scores of histometric analysis for the control group and the HA group were  $2.33 \pm 0.51$ ,  $2.16 \pm 0.40$ , respectively (Table 4; Figs. 1,5).

The granulation tissue was mainly absent in the control group slides sections. On the other hand, the HA group showed scanty to moderate granulation

tissue response; the mean scores for granulation tissue formation in the control group and the HA group were  $(1.833 \pm 0.40$ ,  $2.33 \pm 0.51$ ) respectively (Table 4) (Figure 1,6).

**Table 4:** Histopathological finding scores of skin wound healing at the first day (mean and standard deviation):

Day 1	Inflammatory C. I.	Granulation T. F.	Re-epithelialization
Control	$2.3333 \pm 0.51640$	$1.8333 \pm 0.40825$	$0.0000 \pm 0.00000$
Hyaluronic acid	$2.1667 \pm 0.40825$	$2.3333 \pm 0.51640$	$0.5000 \pm 0.54772$

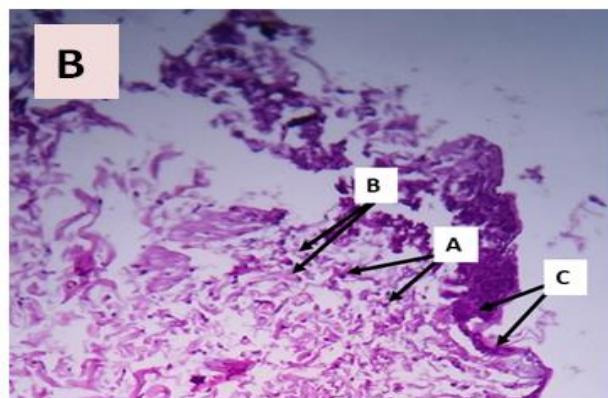
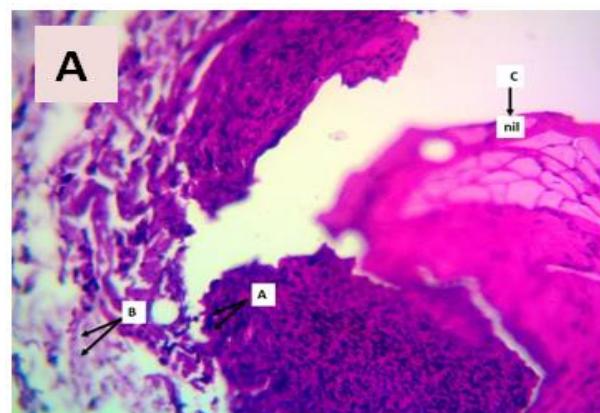


Fig. 1: Photomicrograph of skin wound in (A) control group and (B) hyaluronic acid at 1<sup>st</sup> day.

A: inflammatory cell infiltration

B: granulation tissue formation

C: Re-epithelialization.

### On the third day after surgery:

The inflammatory response in the Control group showed a mild inflammatory response. In contrast, slide sections of the HA group displayed a moderate inflammatory response. The mean score of inflammatory response was  $(2.00 \pm 0.63)$  in the control group and  $(2.8 \pm 0.75)$  in the hyaluronic acid group (Table 5 and Figs. 2,5).

The granulation tissue assessment in the control group showed little granulation tissue in comparison to the HA group, which showed a moderate amount of granulation tissue, the mean score of granulation in the control group was  $(1.166 \pm 0.40)$ , while the mean of the HA group was  $(2.833 \pm 0.40)$  (Table 5 and Figs. 2,6).

Re-epithelialization in the negative control group appeared covering less than half of the wound in some slides sections and some slides covering more than half of the wound. However, the HA group showed Re-epithelialization covering more than half the wound. The mean value of histological score was  $(1.5 \pm 0.54)$  in control and  $(2 \pm 0.0)$  in the HA group (Table 5; Figs. 2,7).

Two independent samples, Mann-Whitney U Test, revealed a non-significant difference in inflammatory response between groups and a significant difference in granulation and Re-epithelialization between the HA and control groups. The HA group exhibited a greater rate of granulation tissue development and a significant increase in Re-epithelialization.

Table 5: Histopathological finding scores of skin wound healing at the 3rd day (mean and standard deviation):

Day 3	Inflammatory C. I.	Granulation T. F.	Re-epithelialization
control	$2.0000 \pm 0.63246$	$1.1667 \pm 0.40825$	$1.5000 \pm 0.54772$
hyaluronic acid	$2.8333 \pm 0.75277$	$2.8333 \pm 0.40825$	$2.0000 \pm 0.00000$

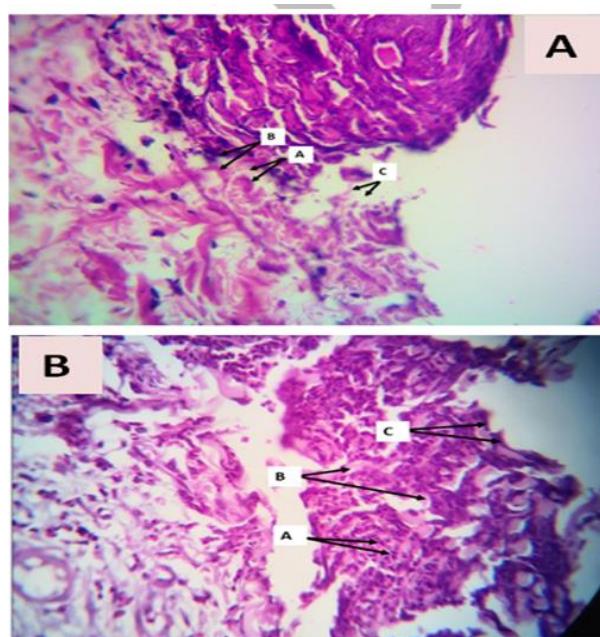


Fig. 2: Photomicrograph of skin wound in (A) control group and (B) hyaluronic acid at 3rd day.  
A: inflammatory cell infiltration. B: granulation tissue formation. C: Re-epithelialization.

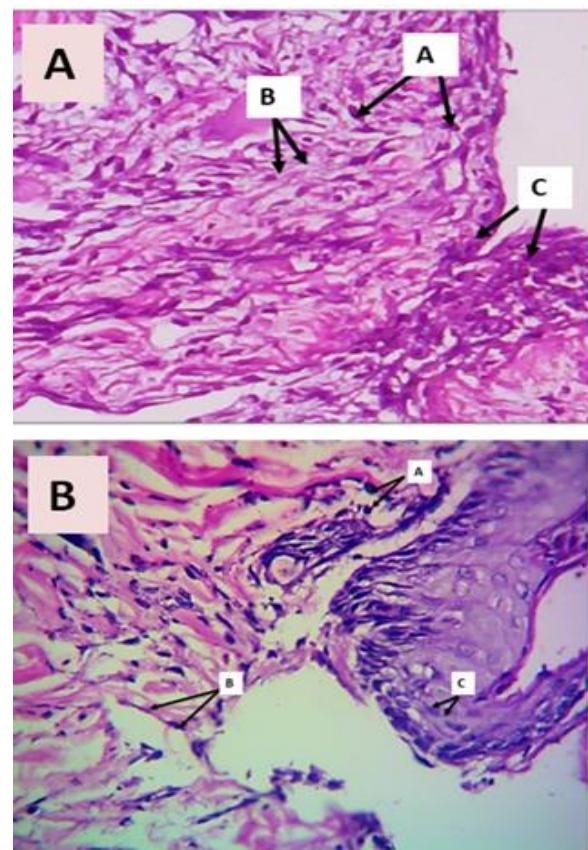


Fig. 3: Photomicrograph of skin wound in (A) control group and (B) hyaluronic acid at 7<sup>th</sup> day.  
A: inflammatory cell infiltration.  
B: granulation tissue formation.  
C: Re-epithelialization.

#### At one week after surgery:

The control group appeared nil in the inflammatory response in some slides and mild in others; some slides of HA showed nil inflammatory cell infiltrate and some showed a mild response; the mean score for HA was  $(1.33 \pm 0.51)$ . The mean score of inflammatory cell infiltrate in HA was  $(1.66 \pm 0.51)$ . (Table 6 and Figs. 3,5).

The Control group displayed scanty granulation tissue in most of the slides. In contrast, Hyaluronic acid slide sections were distributed between a scanty and moderate amount of granulation tissue. The mean value of granulation tissue in the control group was  $(1.833 \pm 0.40)$ , and in the HA group was  $(2.5 \pm 0.54)$  (Table 6 and Figs. 3,6).

The Control group displayed re-epithelialization covering more than half of the wound in almost all slides; the HA group showed good result translated by re-epithelialization covering the entire wound irregular thickness in almost all slides in this group, the mean score of the histological investigation was  $(2 \pm 0.0)$  in the control group. It was  $(2.83 \pm 0.75)$  in the HA group (Table 6 and Figs. 3,7).

Two independent sample Mann-Whitney U Test revealed a non-significant difference in inflammatory response between groups on the 7th day

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of surgery, also revealed a significant difference in granulation and Re-epithelialization between HA group and control group, the HA group exhibiting a greater rate of granulation tissue development and a significant increase in re-epithelialization.

Table 6: Histopathological finding scores of skin wound healing at the 7<sup>th</sup> day (mean and standard deviation):

Day 7	Inflammatory C. I.	Granulation T. F.	Re-epithelialization
control	1.6667± 0.51640	1.8333± 0.40825	2.0000± 0.00000
Hyaluronic acid	1.3333± 0.51640	2.5000± 0.54772	2.8333± 0.75277

### At two weeks after surgery:

The inflammatory infiltration in both groups ranged from nil to moderate control group inflammatory response score was (1.33±0.51), the mean score of HA was (1.166±0.40) (Table 7 and Figs. 4,5).

Both groups at this day showed a closely similar amount of granulation tissue formation; scanty granulation tissue appeared prevalent in most slides sections of both groups. Histological scores of the Control group and HA group were (2±0.63), (2.166±0.75), respectively (Table 7 and Figs. 4,6).

In this period of the study, the re-epithelialization in the control group displayed re-epithelialization covering more than half of the wound with some slides showing the entire wound covering with irregular thickness; HA group showed Re-epithelialization covering the entire wound with normal thickness. The Control group histological score was (2.66±0.51) while the HA group score was (3.66±0.51) (Table 7 and Figs. 4,7).

Two independent samples, Mann-Whitney U Test, revealed a non-significant difference in inflammatory response and granulation between groups on the 14th day of surgery, also revealed a significant difference in Re-epithelialization between HA group and control group, the HA group exhibiting faster Re-epithelialization.

Table 7: Histopathological finding scores of skin wound healing at the 14th day (mean and standard deviation).

Day 14	Inflammatory C. I.	Granulation T. F.	Re-epithelialization
control	1.3333± 0.51640	2.0000± 0.63246	2.6667± 0.51640
Hyaluronic acid	1.1667± 0.40825	2.1667± 0.75277	3.6667± 0.51640

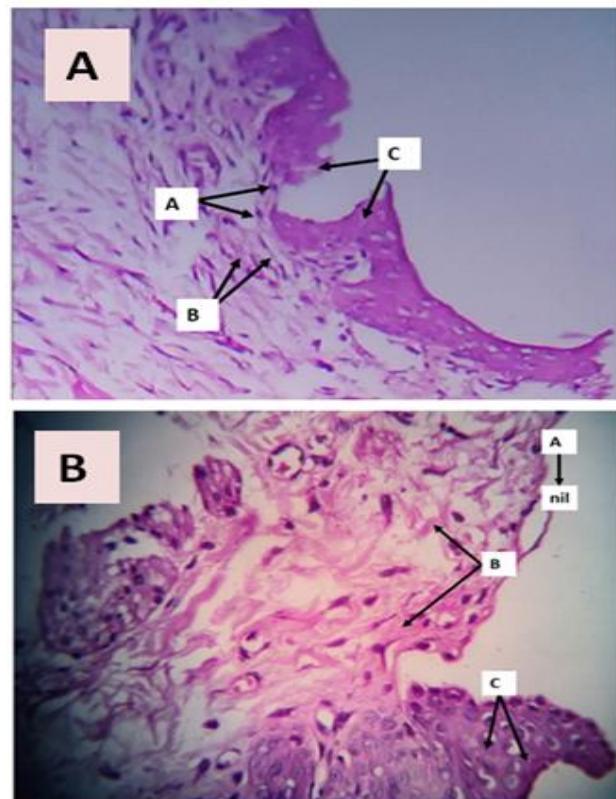


Fig. 4: Photomicrograph of skin wound in (A) control group and (B) hyaluronic acid at 14<sup>th</sup> day.  
A: inflammatory cell infiltration  
B: granulation tissue formation  
C: Re-epithelialization.

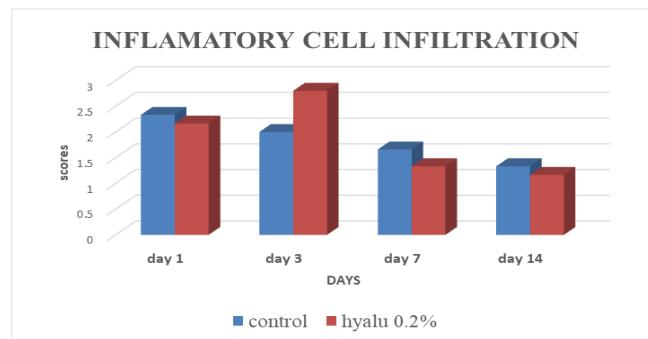


Fig. 5: Inflammatory cell infiltration Scoring at 1st,3rd, 7th, and 14th Days after Incisions.

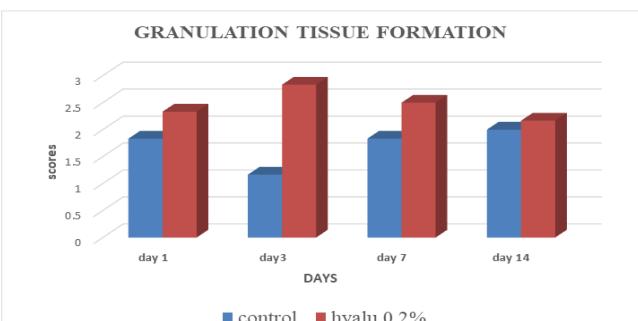


Fig. 6: Granulation tissue formation Scoring at 1st, 3rd,7th, and 14th Days after Incisions.

In the control group, re-epithelialization was at the edge of the wounds. At the same time, some of the HA slides showed re-epithelialization covering less than half of the wound, the mean values of re-epithelialization scores for control and the HA group were ( $0 \pm 0.0$ ,  $0.5 \pm 0.54$ ), respectively (Table 4 and Figs. 1,7). Two independent samples, Mann-Whitney U Test, revealed no significant difference between inflammatory, granulation, and re-epithelialization groups.

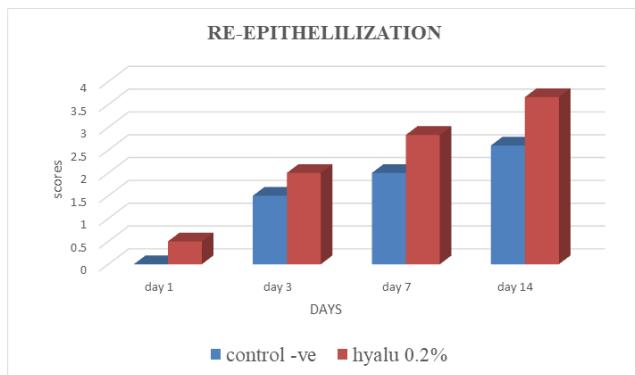


Fig. 7: Re-epithelialization Scoring at 1st,3rd,7th, and 14th Days after Incisions.

## DISCUSSION

Wound healing is critical for survival: it begins soon after damage with hemostasis and seeks to re-establish the epithelial barrier. Following hemostasis, it goes via a series of partially overlapping steps: inflammation, proliferation, and remodeling. The entire process is fragile and vulnerable to interruption, failure, or change, resulting in the creation of non-healing chronic wounds or fibrotic scars and increasing the risk of infection, eventually causing patient morbidity. (Cialdai et al., 2017).

Hyaluronic acid, as an extracellular matrix component, is essential in all stages of wound healing, encouraging cell migration, differentiation, and proliferation while also controlling extracellular matrix architecture and metabolism. (Chen et al., 2019)

In this study, the inflammatory cell infiltrate in the hyaluronic acid group reached the peak on the third day of study then declined during the next two weeks of the healing process; there was no significant difference ( $p \leq 0.05$ ) between the hyaluronic acid group and control group in the inflammatory response, which suggest that the mechanism of action of HA does not affect on inflammatory response during the wound healing process. This result came to parallel with Nyman et al., (2019), who discovered no significant effect for HA on the inflammatory response.

The results of the present study demonstrated that wounds topically treated with HA had enhanced wound healing by enhancing granulation tissue formation, which was significantly increased on the third and seventh day of the study compared to the control group. This result came to parallel with the result of Chen et al., (2019) After applying HA, he discovered a significant increase in Ki-67 expression, particularly in fibroblasts and the basal epidermal layers, as well as a significant increase in VEGF expression in the wound margin area. He also discovered that prolyl 4-hydroxylase expression was significantly elevated in the peri-wound edge, particularly in endothelial cells and fibroblasts., all these factors enhance granulation tissue formation and maturation.

Also, Scarano et al., (2021) found similar findings in his study when he administered HA via dermis injection technique, HA stimulated fibroblast activity, and the synthesis of Type III reticular collagen. Also, HA increased angiogenesis, epidermis thickness with the stratum basal cells' augmentation and increased the Epidermal Growth Factor (EGF).

HA increases the formation of CD44 receptors and improves its enzymolysis, encouraging angiogenesis, increasing collagen expression, and reducing the ratio of collagen types I and III, all of which increase the strength and flexibility of the afflicted skin. ( Zhao et al.,2013; Canciani et al., 2021)

The wounds in this study left to heal secondary intentional healing, the gap in the wound bed filled with a layer fibrin clot. Çankaya et al., (2020) observed that topical HA application on free gingival graft enhances the formation of a well-vascularized layer that works as a scaffold between the donor and recipient sites during the early phases of wound healing, acting as a barrier against tissue tensions leading to promote wound healing process.

The present study showed that HA significantly increased Re-epithelialization in the 3rd,7th, and 14th day, histological evaluation of hyaluronic acid group these results came in concordance with Gao et al., (2019) who demonstrated that the application of HA has the potential of enhancing Re-epithelialization and angiogenesis in the wounds of rats models.

Also, Yıldırım et al., (2018) noticed that topical HA periodontal dressing reduces post-operative discomfort and accelerates epithelization of the palatal donor wound sites. So HA application led to tissue maturation and rapid epithelization and ensured a good

Color Match. Nyman *et al.*, (2019), in their study on the skin, he concluded that exogenous intradermal HA promotes re-epithelialization and changes protein expression in human in vivo deep dermal skin wounds.

## CONCLUSION

Hyaluronic acid cream is considered an ideal material due to its biodegradability and biocompatibility with the skin; hyaluronic acid has a beneficial effect on the acute wound healing process through enhancing granulation tissue formation and re-epithelialization.

## Declaration of Conflicting Interests

The authors revealed that there is no potential conflicts of interest.

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