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A Novel Chitosan-Based Gel for Burn Wounds

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Abstract

Burns are the most common injuries caused by exposure to various sources of heat or chemicals. The epidermis consists of 95% keratinocytes which are responsible for controlling the distribution and amount of melanin pigment in melanocytes. The aim of the present study was to establish the effectiveness of a novel chitosan-based gel on the acceleration of wound healing and the original restoration of keratinocytes and melanocytes.

In this study, second-degree burn wounds were induced using seal aluminum on two different groups of rabbit, of which one group was treated using sterile gauze and the other was treated with a chitosan-based gel, named ChitoHeal®. Histopathology tests and scanning electron microscope (SEM) and transmission electron microscopy (TEM) results confirmed complete normal restoration of the epidermis, and there was no change in pigmentation and melanocyte overgrowth in the epidermis and keratinocytes. The study exhibited that complete wound healing process with normal structured keratinocyte cells and pigmentation would take place after applying ChitoHeal® gel.

1 Introduction

1.1 What Is Burn Wound?

Burns are one of the most common injuries in both children and adults [1, 2]. Although the mortality rate from burns has declined in the past decade; however, it is still high in some countries. When more than 70% of the body surface is affected by burn wounds, it may be fatal [3]. The classification of burns is according to the depth of the injury. Epidermis and partial dermis damage is classified as first-degree burns [4]. When the dermis is damaged in large scale, it is considered as second-degree burns. This type of burn causes the skin to blister and becomes extremely red and sore. When the entire skin and hypodermis are damaged, it is classified as third-degree burns. In fourth-degree burns, the skin, hypodermis, and even bones are largely damaged.

1.2 Importance of Healing Burn Wound

1.2.1 Inflammation

Inflammation is vital to initiate the process of burn wound healing, and inflammatory mediators such as cytokines, kinins, lipids, etc. provide immune signals to recruit leukocytes and macrophages that initiate the proliferative phase [3]. Meanwhile aberrant inflammatory pathways have been linked to hypertrophic scarring, and anti-inflammatory treatments could potentially aggravate symptoms and delay wound healing [4]. In the proliferative phase wound, reepithelialization is activated via keratinocyte and fibroblast [4]. Significant edema that is initiated by several factors including vasodilation, extravascular osmotic activity, and increased microvascular permeability often accompanies inflammation [5].

Treatment of inflammation in large burns is difficult. Early excision and grafting have become the gold standard for treatment of full and deep partial-thickness burns [5], in part because early excision helps reduce the risk of infection and scarring [5].

1.2.2 Infection

The skin functions as a barrier to the external environment to maintain fluid homeostasis and body temperature while providing sensory information along with metabolic and immunological support. Damage to this barrier following a burn disrupts the innate immune system and increases susceptibility to bacterial infection [4]. Burn wound infection was defined in a rat model with *Pseudomonas aeruginosa* [4, 5], in which the following progression was observed: burn wound colonization, invasion into subjacent tissue within 5 days, destruction of granulation tissue, visceral hematogenous lesions, and leukopenia, hypothermia, and death.

Burn patients are at high risk for infection [6], especially drug-resistant infection [5], which often results in significantly longer hospital stays, delayed wound healing, higher costs, and higher mortality [5, 6]. Infection can lead to the development of a pronounced immune response, accompanied by sepsis or septic shock, which results in hypotension and impaired perfusion of end organs, including the skin—all processes that delay wound

healing. Furthermore, the leading causes of death following a severe burn are sepsis and multiorgan failure [4, 5, 6], so prevention and management of infection are a primary concern in the treatment of burn patients.

Application of chitosan-based gel (ChitoHeal® gel) is for burn wound healing. Chitosan is a polysaccharide comprising copolymers of glucosamine and *N*-acetylglucosamine. It is derived by partial deacetylation of chitin from crustacean shells [7, 8]. Chitosan gel also acts as an ideal wound dressing. It is biocompatible, biodegradable, hemostatic, and antibacterial, and more importantly it accelerates wound healing [9]. A previous study showed that chitosan-treated wounds were epithelized when compared with wounds of the control group after the treatment [10].

Animal models have been used to investigate burn wound pathology, local therapy [11], the influence of systemic drug application on the burn wound, and the effect of burn trauma on the entire organism [12]. Guinea pigs [13, 14, 15], Sprague-Dawley rats [16, 17, 18, 19, 20, 21], Wistar rats [22], Long-Evans rats [23], and gold hamsters [24] have been used in burn research. A further commonly used animal in burn experiments is the pig [25, 26, 27]. The hairless porcine skin is very similar to human skin. However, pigs pose practical problems as research subjects. They need more housing space and are more expensive to maintain than smaller animals.

Rabbits were chosen in the following study mainly for two reasons. Firstly, New Zealand white rabbits have been shown appropriate for burn studies [28, 29, 30]. Secondly, rabbits are large enough to obtain adequate blood samples for several days without impairing their general condition. Furthermore they are easy in terms of handling and housing and cost less than laboratory pigs. The structural configuration of the skin layers in rabbits is similar to human skin [31]. In humans and other mammals, there are regional differences in the thickness of skin layers as well as in the distribution of hair follicles and sweat and sebaceous glands. The skin of rabbits is more elastic than human skin. However, this difference does not interfere with the usefulness of this model to study the phenomenon of burn depth.

The present studies describe the efficacy of chitosan-based ChitoHeal® gel on accelerating the rate of burn wound healing in animal model.

2 Technique

Experimental design and treatment of animals were approved by the Animal Care Committee of Islamic Azad University, Science and Research Branch. The animals were kept under veterinary supervision and given adequate food.

2.1 Animals

Following the guidelines and recommendations of the Animal Research Board of the American University of Beirut, eight New Zealand rabbits with a weight range of 1.8–2.0 kg were used in this study, designed to continue for 30 days after the experimental burns were inflicted.

The animals' backs were shaved with a standard electric shaver 3 days before the experimental burn. Just before inflicting the burn, the area was depilated with a commercial depilatory cream to obtain smooth and hairless skin. The animals were kept under standard laboratory conditions with veterinary supervision and no restrictions on water and food.

2.2 Anesthesia

The animals were anesthetized by intramuscular injection of 3 mg/kg ketamine and 5 mg/kg xylazine 2% (Chanazine). Booster injections of up to half of the initial dose were administered as needed, in order to ensure that the rabbits were pain-free during the procedure and subsequent application of the dressing.

2.3 Burn Injury

A round aluminum stamp, described by Knabl et al. [32], measuring 4 cm in diameter and 81 g in weight was heated to 80 °C. It was then applied for 14 s with no extra pressure on the skin to produce a superficial, partial-thickness burn (SPT). In each animal, one SPT burn was produced on the vertebral and paravertebral area 10 cm from the tail and 14 cm from the last cervical vertebrae (Fig. 1).

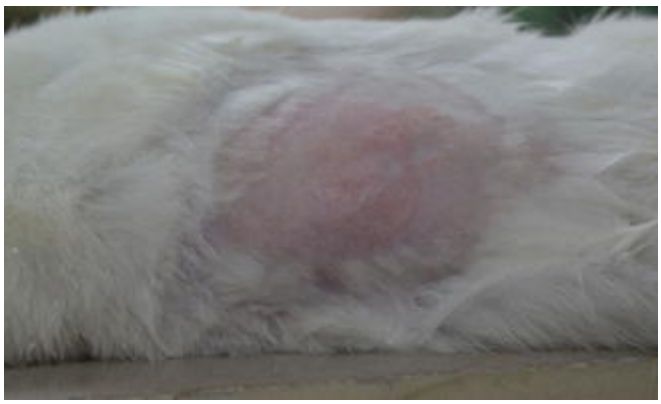


Fig. 1

Burn infliction area

2.4 Treatment

The animals were divided into two groups. Group 1 was the control group, in which the burn wounds were covered by sterile gauze dressing. Group 2 received a daily application of a chitosan-based gel covered with sterile gauze dressing. The chitosan-based gel was applied with a thickness of about 1 mm. Both treatment and control group wounds were then covered by a wraparound bandage.

2.5 Change of Dressing

The dressings were changed daily, after sedating the rabbits with an intramuscular injection of 0.4 mL/kg of 2% xylazine, for the 30-day treatment period. Before the application of a new dressing, the wounds were cleansed with saline solution for both groups.

2.6 Burn Tissue Assessment

Punch biopsies were taken from the center of the burn areas along with small bits of normal skin from around the wounds on days 10, 20, and 30 from both groups. The biopsied tissues were cut into two halves: one was fixed in 10% formalin for routine microscopy staining and the other half was fixed in 2.5% glutaraldehyde for analysis by scanning electron microscope (SEM) and transmission electron microscopy (TEM), respectively.

The specimens for light microscopy were processed according to standard methods and stained with hematoxylin and eosin. The harvested specimens were fixed in 10% formalin for 24 h. After conventional ethanol gradient dehydration, the tissues were embedded in paraffin and sectioned at 5 mm for hematoxylin and eosin staining.

2.7 Other Assessments

Morphological, histological, and molecular parameters were used to evaluate the efficacy of chitosan-based gel on SPT burns in the treatment group, compared with a gauze dressing used in the control group.

Immediately after the burn was inflicted on the rabbits, the burned tissue was biopsied. The biopsied tissue was fixed in 10% formalin. After light microscopy assessment, the pathologist confirmed an SPT burn. Based on the TEM protocol, the cell nucleus was stained with uranyl acetate, and the cell cytoplasm was stained with lead citrate.

Body mass index (BMI) was calculated using the Lee formula:
$$ \mathrm{BMI}=\mathrm{BW}1/3\left(\mathrm{g}\right)/\mathrm{nasoanal}\ \mathrm{length}\ \left(\mathrm{cm}\right) $$

2.8 Results

Morphological, histological, and molecular parameters were used to evaluate the efficacy of ChitoHeal® gel on superficial partial-thickness burns in treatment group compared to a gauze dressing used in the control group.

2.8.1 Macroscopic Assessments

Lee index (body mass index)

Body mass index was calculated using the Lee formula (1):
$$ \mathrm{BMI}=\mathrm{BW}1/3\left(\mathrm{g}\right)/\mathrm{nasoanal}\ \mathrm{length}\ \left(\mathrm{cm}\right) $$
(1)

On day 10, the Lee index noticeably declined in both groups. The decline in this index, resulting from trauma-based weight loss, was expected. In time, the Lee index improved in all groups, due to the progression of wound healing and reduction of stress (Figs. 2 and 3).

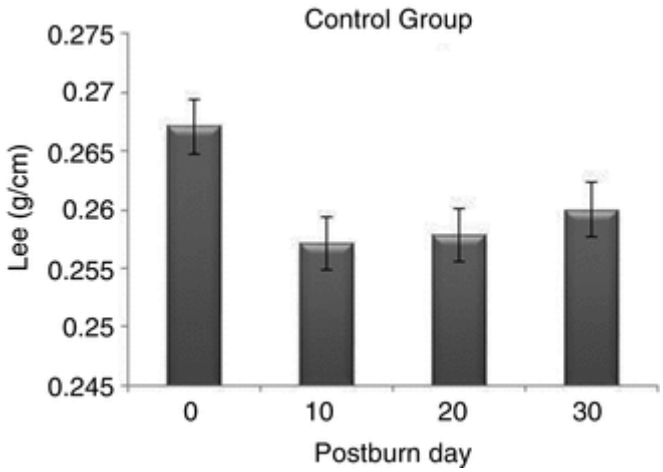


Fig. 2

Lee index for control group

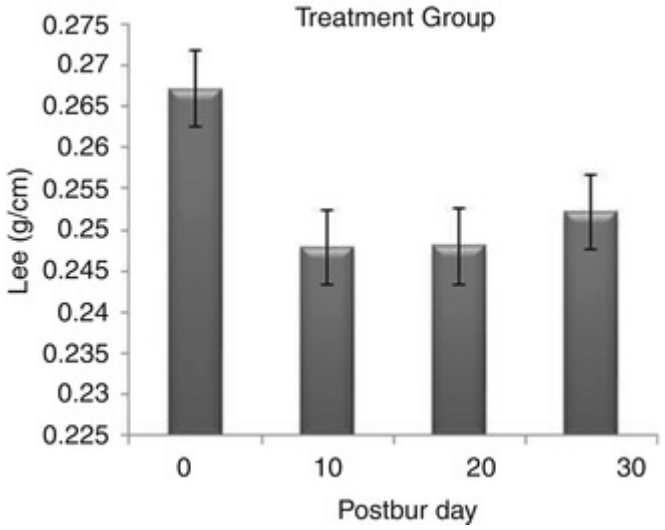


Fig. 3

Lee index for treatment group

2.8.2 Wound Edge Migration Rate Assessment

The area and periphery of the wounds were calculated using digital photographs and the Auto CAD program. Wound edge migration rate was calculated using Gilman's modified Eq. (2):

$$ \begin{array}{c}\mathrm{WEMR}\ \left(\mathrm{mm}/\mathrm{day}\right)\\ {}=\left\{\left(Ab- Aa\right)/\left(\left[Pa+ Pb\right]/2\right)\right\}/\left(b-a\right)\end{array} $$

(2)

In this equation, *A* represents area, *P* represents periphery, and *a* and *b* represent the start and end days of observations.

The area and periphery of wounds treated with ChitoHeal® gel were smaller than the wound area and periphery in the control group (Figs. 4 and 5).

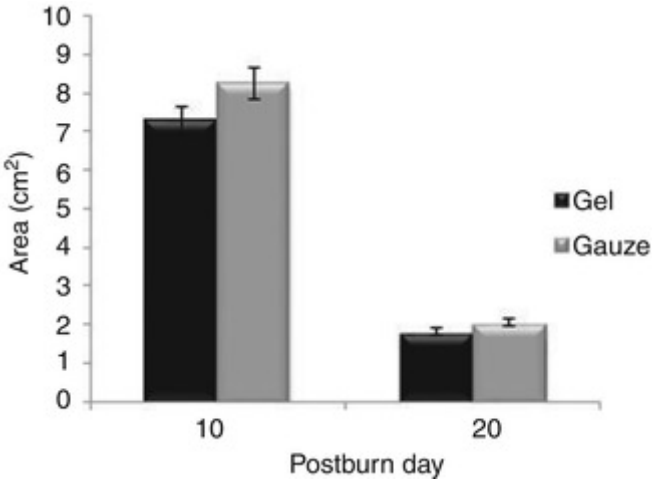


Fig. 4

Wound area—post-burn day

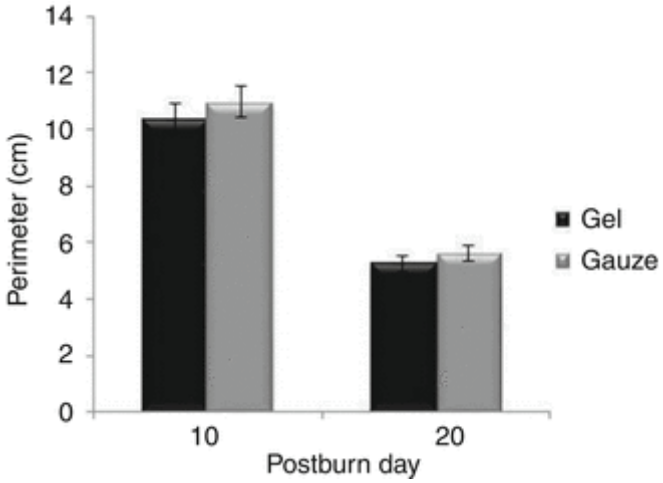


Fig. 5

Wound periphery—post-burn day

Wound edge migration in the treatment group was noticeably higher than that in the control group as shown in Fig. 6. In the proliferation phase in wound, which occurs after synthesis and deposition of intra cellular matrix, the division, differentiation, and migration of epithelial cells begin. As ChitoHeal® gel accelerated wound closure, it seems it has induced all stages of the proliferation phase, especially cell migration, due to the moist environment which it provides, allowing the cells to move more easily and farther.

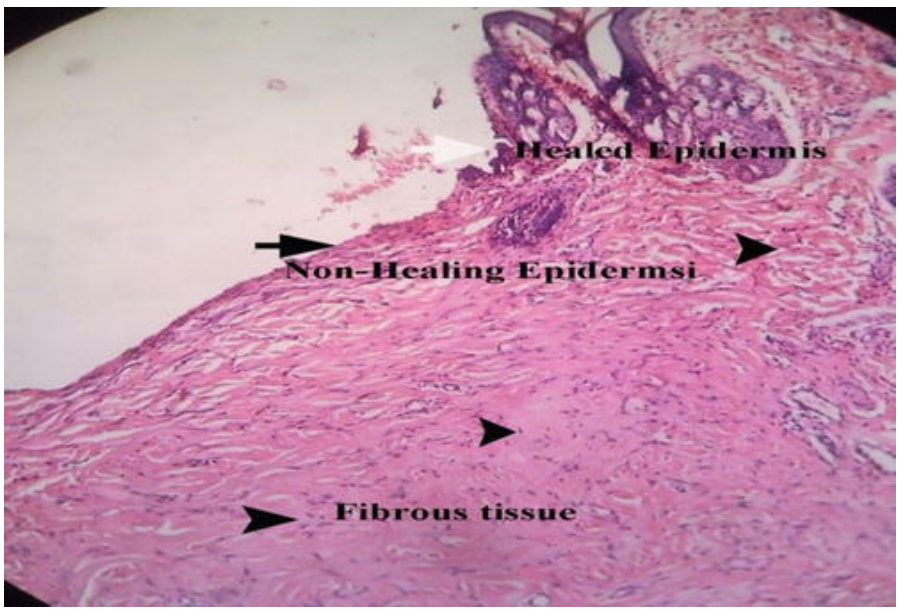


Fig. 6

Treated specimen, day 10

2.8.3 Clinical Assessment

On days 2 and 5, the scabs on the wounds in the treatment group were thicker than those in the control group. The necrotic tissue, however, was completely adhered to the wound, and its underside was soft and flexible. This indicated the rapid healing process, since the faster the damaged tissue degrades, the more quickly the wound bed clears, and healing enters the next phase. The softness of the scab in the treatment group in comparison with that of the control group may well be associated with the application of the chitosan-based gel dressing.

2.8.4 Histopathology

In the light microscopy assessment of normal skin, intact epidermis and dermis were distinguished. Melanocytes were irregularly present among keratinocytes. Since rabbit skin is more flexible than human skin, a large number of elastin fibers were observed.

On day 10, no reepithelialization was observed. The epidermis was present only in necrotic and ulcer forms. In the dermis, both fibrous and granular tissues were observed, a sign of the progression and matrix deposition processes. Hemostasis and inflammation precede epidermal cell proliferation, and the presence of inflammatory cells and coagulation phase residue was considered normal (Fig. 6).

There was less inflammation (33%) in the treated group on day 10 compared with the control group, suggesting that the chitosan-based gel decreased the inflammatory reaction. Less inflammation results in less collagen synthesis and deposition and, therefore, less scar formation. In the control group on day 10, granulation was observed. The epidermis was not reconstructed, ulceration was noticeable, and inflammation continued.

On day 20, in the treated group, proliferation of epidermal cells was observed. Reepithelialization was completed, and the epidermis was healed and had a near normal appearance. Furthermore, all wounds showed almost complete epidermis reconstruction, while 50% of the control group specimens showed ulcers and poor or partial reconstruction of the epidermis. The acceleration of healing in the treatment group was confirmed microscopically. In the group, 67% of wounds healed; however, there was no trace of hair follicles. In the control group, 50% of wounds healed (Fig. 7). The epidermis in the control group appeared to be partially reconstructed; however, ulceration was observed. The epidermis thickness seemed to be thin, and inflammatory cells were present in the dermis. The formation of wound bed, before epidermis formation in the expected healing direction, from depth to surface, was observed (Fig. 7).

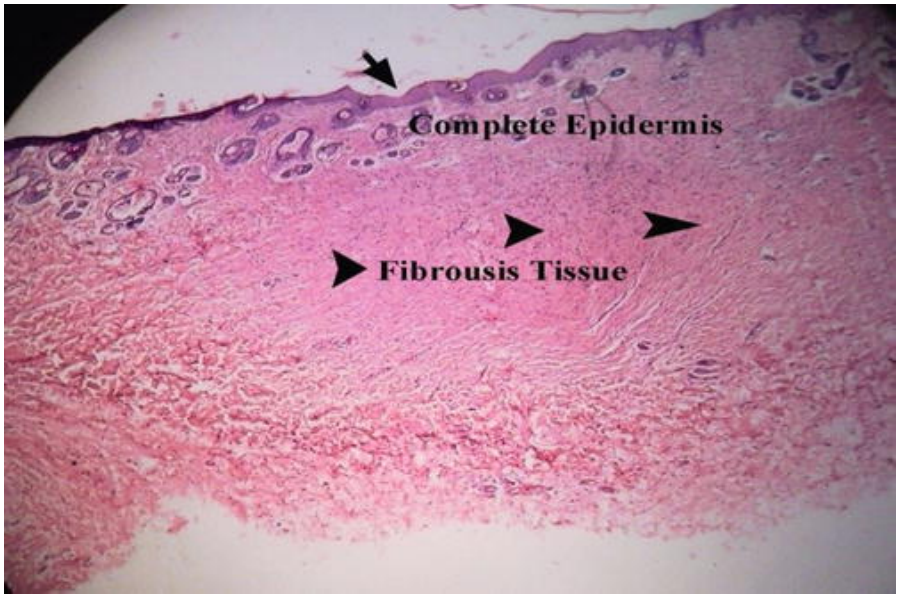
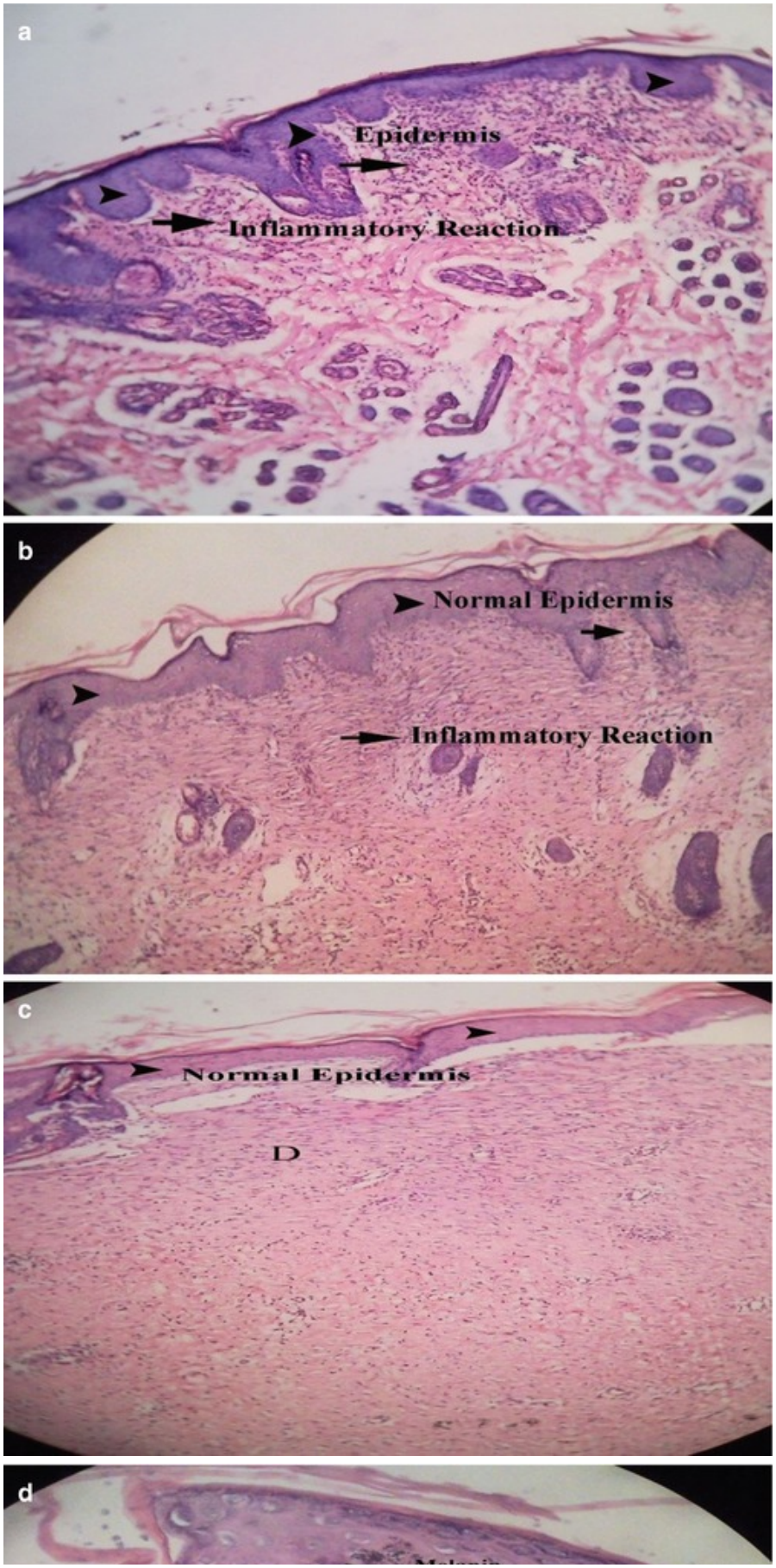


Fig. 7

Treated specimen, day 20

In the treated group, by day 30, the epidermis was thoroughly reconstructed and was a normal thickness. There was no melanocyte overgrowth, indicating the absence of hyperpigmentation and the restoration of normal color of the skin. In some cases, swelling in keratinocytes was observed; that was due to their moisture absorption as a result of the moist wound healing environment provided by chitosan-based gel. Inflammation had mostly disappeared. Epidermis growth and the number of keratinocytes appeared to be normal (Fig. 8). In the control group, by day 30, the epidermis was reconstructed. There was papillary growth in the wound bed, which could be associated with hyper-keratinocytes expression.


a
Epidermis
Inflammatory Reaction
b
Normal Epidermis
Inflammatory Reaction
c
Normal Epidermis
D
d

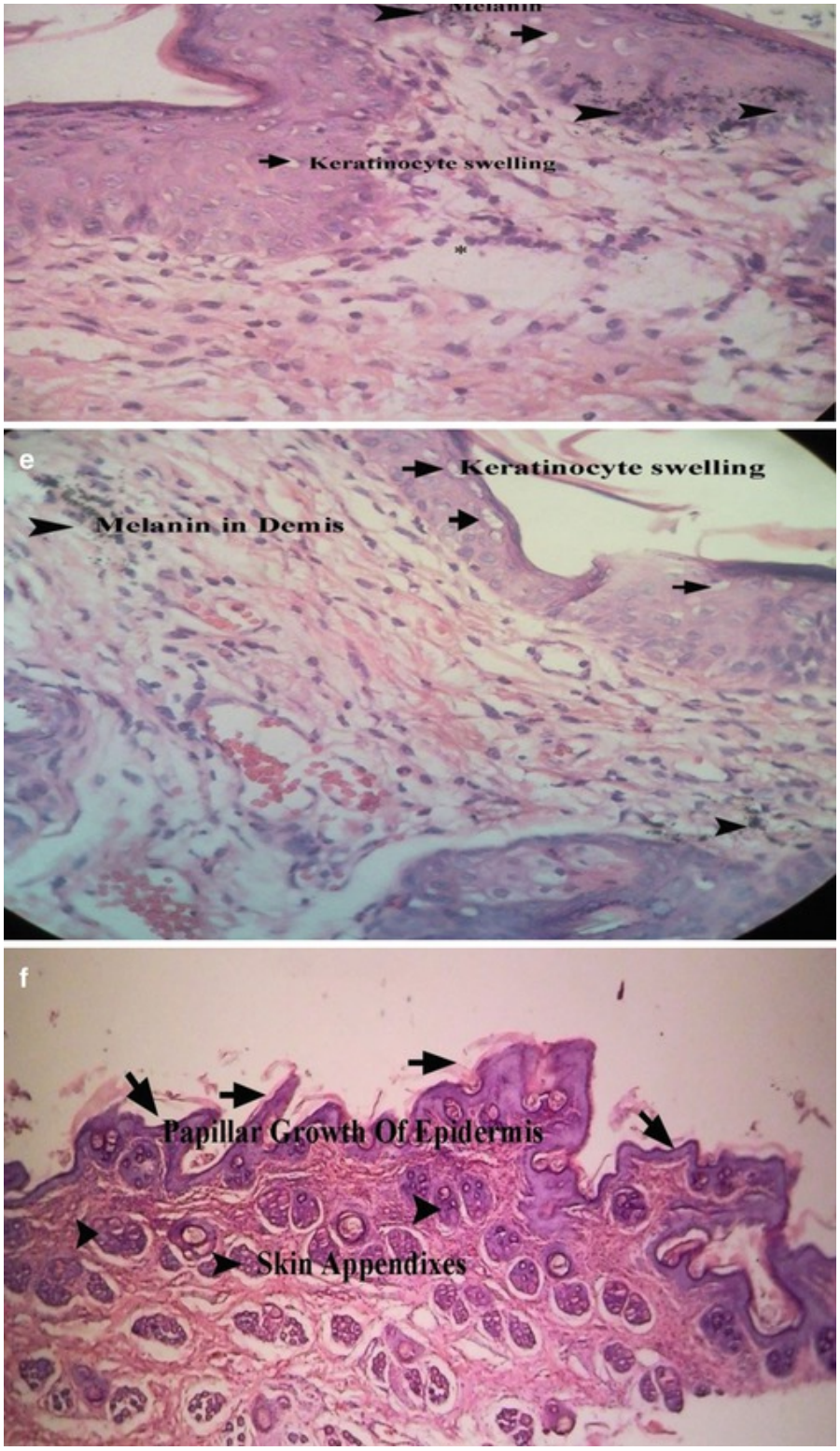


Fig. 8

(**a**–**c**) Treated specimen, day 30. (**d**–**f**) Control specimen, day 30

There were numerous active melanocytes, and melanin was dispersed in the stratum spinosum of the epidermis and dermis. A number of keratinocytes appeared swollen. The epidermis displayed a higher than normal thickness in the control group, comparing the light microscopy images to that of the treatment group. This indicated an abnormal healing in the control group (Fig. 8).

2.8.5 Microscopic Assessment

Scanning Electron Microscopy

Melanocyte Investigation

On the tenth day of healing, it was noticed that fibrous tissue was present in both treatment and control groups. Fibroblasts were the main cells present, and the inflammatory phase was almost over. In SEM images of both the control and treatment groups on day 10, small immature cells together with tissue granules were noticeable, indicating the start of the cell proliferation and tissue granulation phases. In the control group, the presence of blood and inflammatory cells was more noticeable, indicating a longer inflammatory phase in the control group (Fig. 9).

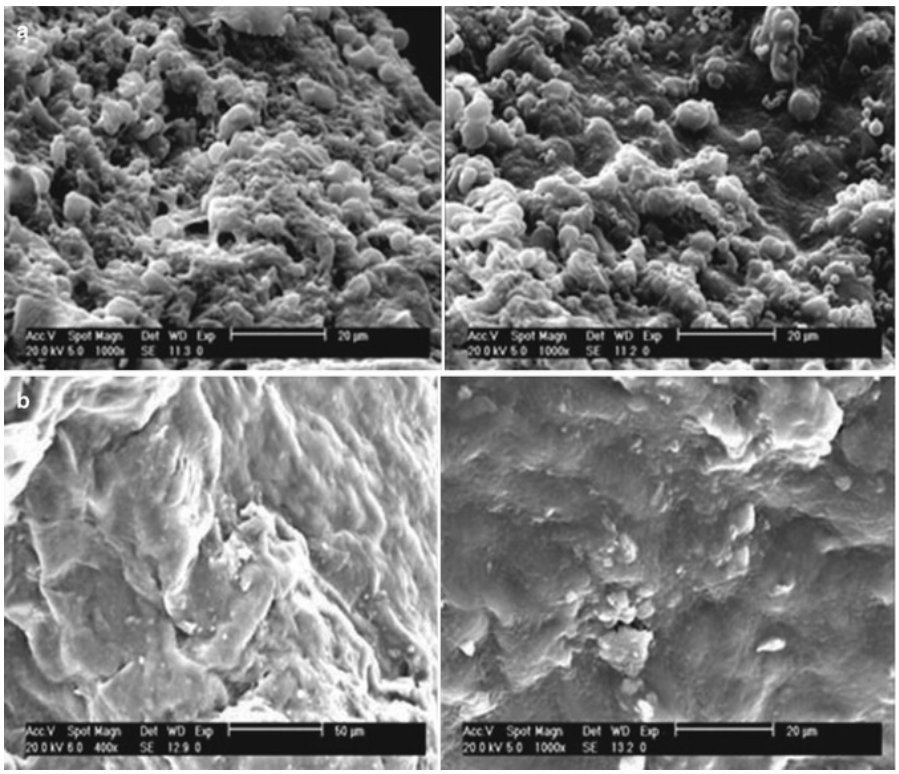


Fig. 9

(**a**) SEM images of control group day 10. (**b**) SEM images of treatment group day 10

On day 20 the wounds were mostly healed in the treatment group. As the epidermis was reconstructed, keratin fibers were detectable. In the dermis of treatment group, some immature granules were present, showing the accelerated reepithelialization and formation of epidermis. The epidermis in the treatment group was more intensified before the dermis was completely mature. In the control group, less keratin was noticed (Fig. 10).

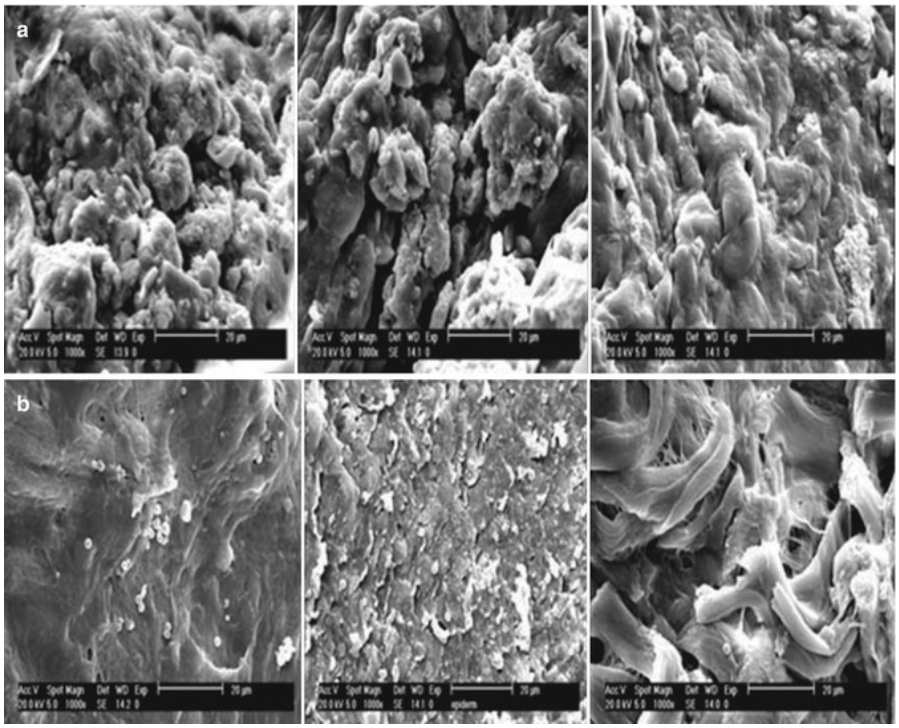


Fig. 10

(**a**) SEM images of control group day 20. (**b**) SEM images of treatment group day 20

On day 30, keratin, representing the reconstructed epidermis, and contracted mature granular tissue, representing the reconstructed dermis, were noticeable in the treatment group. Red blood cells indicated effective angiogenesis. In the control group, tissue granules were still visible. There were little keratins as compared to the treatment group, indicating poor epidermis reconstruction (Fig. 11).

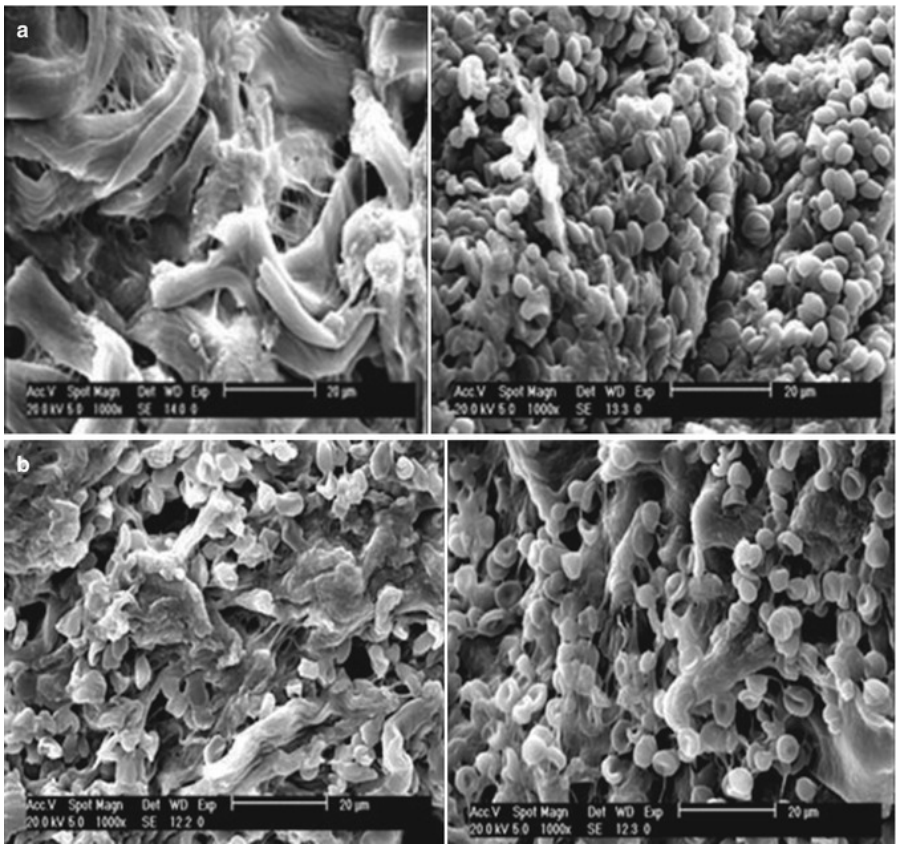


Fig. 11

(**a**) SEM images of control group day 30. (**b**) SEM images of treatment group day 30

Keratinocyte Investigation

The scanning electron microscope was used for observation of the morphology of the cells. A control and a treated sample SEM pictures are presented from the tenth, the twentieth, and the thirtieth days in Figs. 12, 13, and 14.

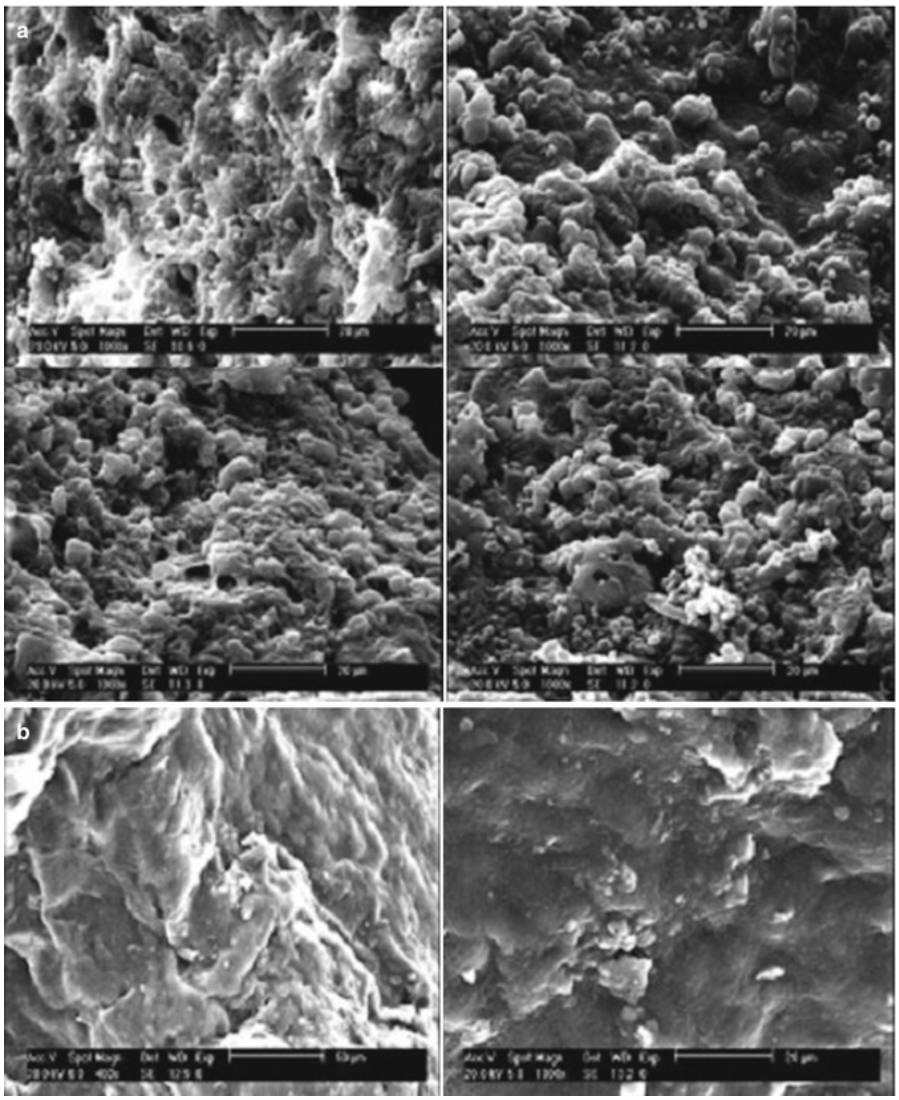


Fig. 12

(**a**) SEM images of control group day 10. (**b**) SEM images of treatment group day 10

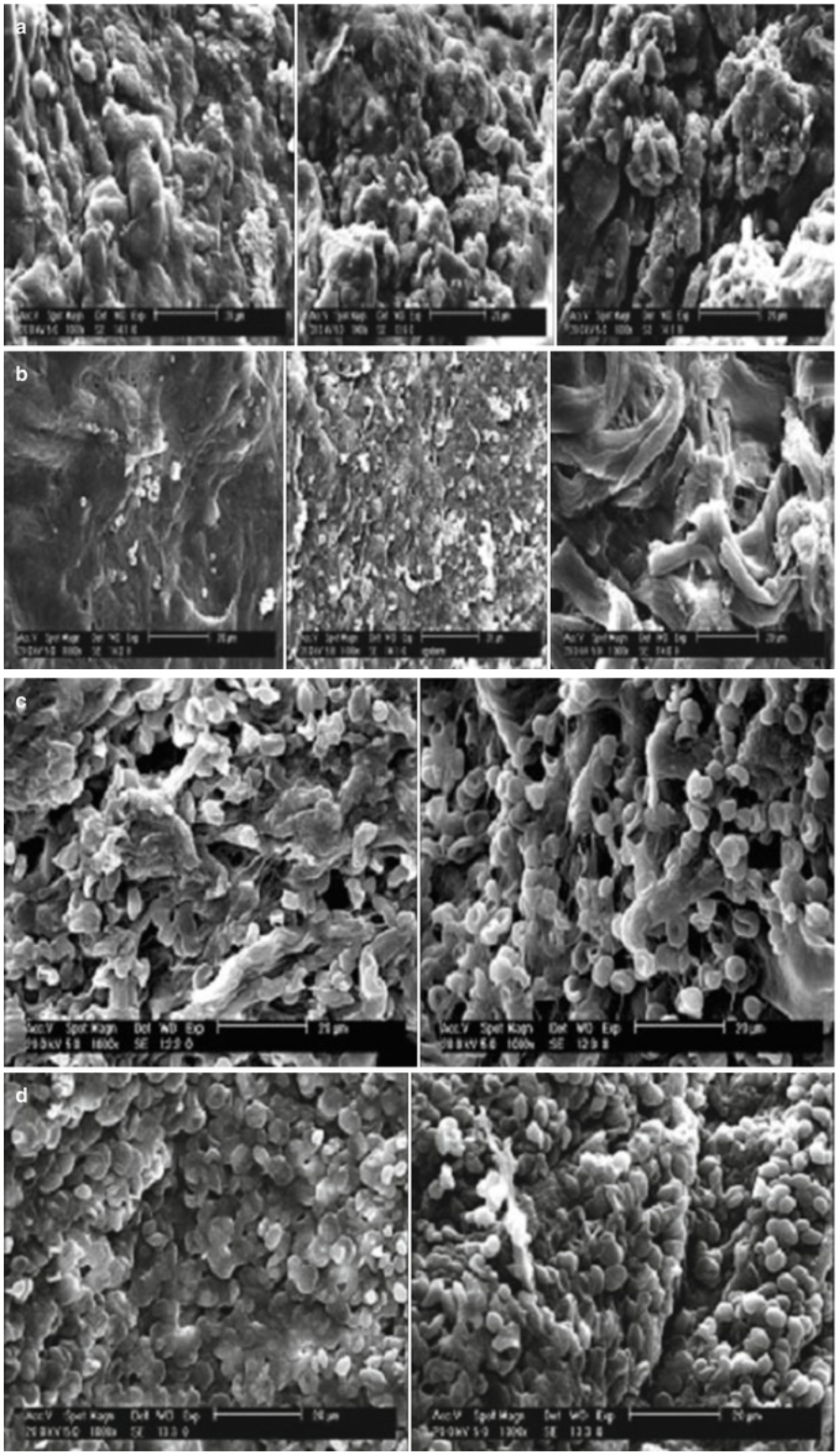


Fig. 13

(**a**) SEM images of control group day 20. (**b**) SEM images of treatment group day 20. (**c**) SEM images of control group day 30. (**d**) SEM images of treatment group day 30

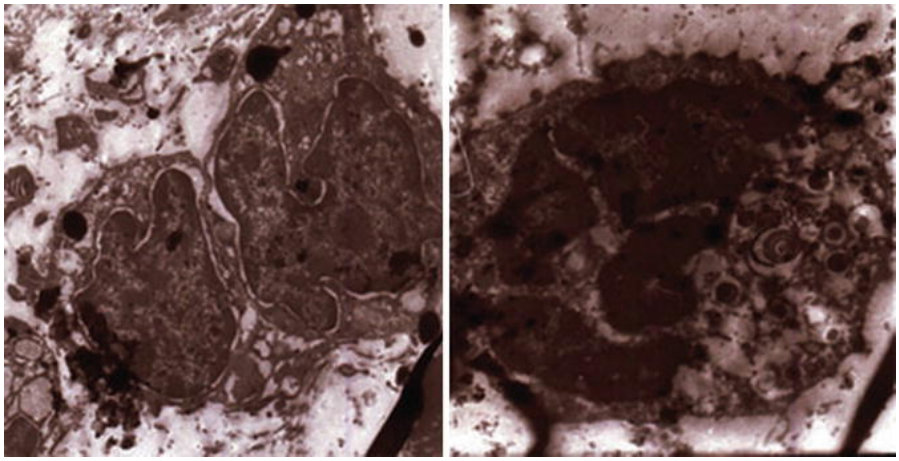


Fig. 14

TEM images of melanocyte cytoplasm in treatment group day 30

In general, on the tenth day of repair, wounds were in the process of contraction. Matrix and fibrous tissue were produced. Therefore, fibroblast and protein strings were observed for the most part.

A series of small and immature cells were observed in the SEM pictures of the control and experimental samples from the tenth day indicating cell division and production of granulation tissue. These cells were observed in pictures of both samples. There were greater presence of blood and inflammatory cells in control samples than treated cells indicating longer inflammation stage in control sample in comparison to the treated sample.

Repair of superficial burn wounds were almost completed by the 20th day. As indicated by the microscopic and histopathology results, repair was in the treated samples, and epidermis and dermis layers were noticed in the treated group.

However, in control samples, fewer keratin fibers were observed. In other words, these cells and tissue have not reached maturation. Therefore, fewer repairs were in the control samples.

On the 30th day, repair was completed, and wounds were completely closed, and epidermal and dermal layers looked normal especially in the treated group. Due to slower rate of repair in the control group, the epidermis layer appeared thinner with lower density. The dermis did not show any signs of the repair of blood capillaries. Blood flow seems normal and lower in the treated samples since repair process is ending.

Transmission Electron Microscopy

Melanocyte Investigation

Using TEM, melanocytes were observed in the treatment group (Fig. 14). As a result of reepithelialization, melanocytes were present among the keratinocytes. The morphology of the melanocytes was normal, implying that, in appropriate wound healing, epidermal melanocytes are reconstructed.

Keratinocyte Investigation

As illustrated in Fig. 15, keratinocytes were present next to melanocyte cells. These pictures showed keratinocyte layers producing epidermis cells. Considering rate of healing in treated group, it appears that ChitoHeal® gel has caused the acceleration of reepithelialization and production of normal epidermis containing keratinocyte cells. As evident from the images, morphology, shape, and composition of these cells appear normal.

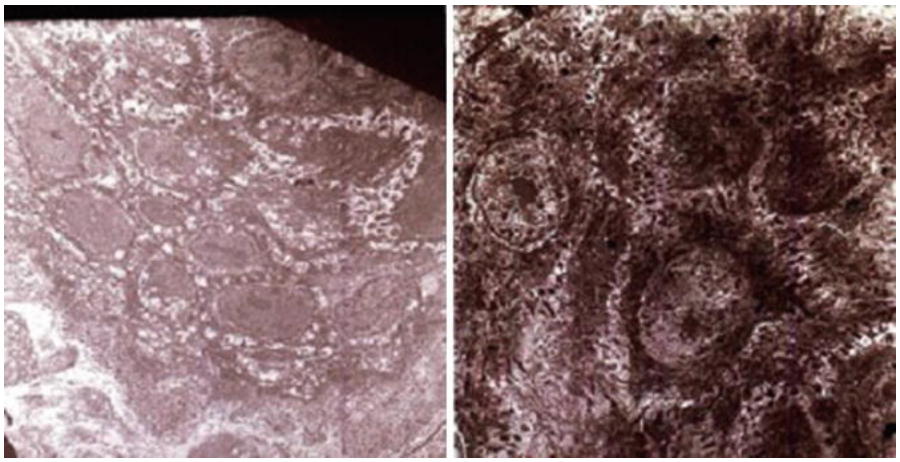


Fig. 15

TEM images of keratinocyte next to melanocyte cells in treatment group day 30

These fibers indicate epidermal repair and presence of active and normal keratinocytes in repaired tissues.

3 Discussion

The mammalian epidermis is a stratified, multilayered epithelium, consisting of the interfollicular epidermis and associated appendages, which extend into the dermis and include hair follicles, sebaceous glands, and sweat glands [5]. The epidermis is made almost entirely of keratinocytes (95%). Other cell types found include melanocytes, Langerhans cells (dendritic cells), and Merkel cells (sensory receptors). The epidermis is a dynamic epithelium that is constantly renewed throughout life. Its turnover is

estimated at about 60 days in humans. The aim of this study was to investigate about keratinocyte and melanocyte cells behavior and morphology after wound healing using ChitoHeal® gel in comparison with traditional methods.

The use of ChitoHeal® gel, which is based on chitosan, has improved the rate of wound healing in burn wounds. In fact the application of bioactive dressings consisting of different biomaterials, natural or synthetic, is becoming more widespread in modern wound care treatment [19, 20] as it has been demonstrated by Archana et al. [33]. Application of chitosan and chitosan blend dressing is effective in accelerating burn wounds healing [21].

Results in animals' burn wounds in treatment group compared to control group indicate that ChitoHeal® gel has accelerated the rate of wound healing, the formation and deposition of fibrous matrix, as well as the proliferation and migration of epithelial cells toward the center of the wound. Since epithelial cells proliferate from the wound edges toward its center, as wound heals, its dimensions decrease. Thus, a faster wound closure, with recovering epithelial, shows a satisfactory rapid healing.

The results of the present study demonstrated that the application of ChitoHeal® gel in treatment group has accelerated the rate of wound healing process as compared to the control group where traditional gauze dressings were used.

Conclusions

The outcome of the present study is likely to be important for the development of novel strategies for wound healing, since it sheds light on the potential of the therapeutic regimens. Faster wound healing and reepithelialization of burn wound could result in the reduction of collagen deposition hence preventing severe scar formation.

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