Al-Qadisiyah Journal of Veterinary Medicine Sciences
(P-ISSN 1818-5746/ E-ISSN 2313-4429)
www.qu.edu.iq/journalvm

Efficacy of Lyophilized Urinary Bladder submucosa on open wounds healing

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Abstract

The study's objective was to assess the effectiveness of Lyophilized Urinary Bladder Submucosa in the healing of open wounds. Study subjects included 60 mature, white New Zealand rabbits. All of the animals were housed in same bedding and environmental circumstances. They divided into two groups (n = 30). After general anesthesia and prepared for aseptic surgery, a punch used to make circular full-thickness (1.5 cm) skin incision on the backs of the animals. The rabbits were sorted into two equal groups at random. Histopathological specimens were collected at 7, 14, and 21 days after wounding. Group 1 served as a control group for untreated wounds. Lyophilized bovine UBM was used as a scaffold in Group 2 to treat wound on the first day following surgery, whereas 2gm of UBM hydrogel was applied topically once daily from the second day for 7 days. Fresh urinary bladder was used to form UBM as a lyophilized scaffold and hydrogel was made for treatment of group 2. Due to the hyperplasia of the epidermal layers. In the dermis, tiny collagen fibers replace the injured tissue and encourage the growth of new blood vessels and inflammatory cells. At day 21, G2 demonstrated the development of a keratinized layer over the epidermis. The epidermal layers seemed hyperplastic, and the two skin wound edges appeared to be linked. The dermis has a network of fibrosis and collagen that is regularly arranged and new blood vessels. Additionally, there were fresh, tiny hair follicles in the area of the wound.

Keywords: Lyophilized, Urinary Bladder, submucosa, wound, healing.

Introduction:

Wounds are among the most common health problems, and the cost of wound care and healing has continued to increase in most countries in the world at last decades . In the fields of tissue engineering and regenerative medicine, the ability to produce functional tissues and organs as replacements for their damaged or diseased counterparts is a field that is growing quickly (1). The discovery of cytokines, growth hormones, and potent functional proteins inside the ECM has led to the description of the ECM as a sort of virtual information highway between cells. The idea of "dynamic reciprocity" between intracellular cytoskeletal and nuclear components and the ECM has gained widespread acceptance. An effort has recently been made to apply this phenomenon to the therapeutic usage of the ECM as a scaffold for tissue engineering applications. (2). They have a distinctive 3D surface protein architecture that promotes host cell integration and natural porosity. This expands the surface available for host cell adhesion, proliferation, and migration as well as facilitating the movement of gases and metabolites. These qualities enable biological scaffolds to swiftly interact with host tissue and speed the creation of new tissue (3). These biologic properties can be preserved in biologic scaffolds produced by methods that preserve the composition and structure of the matrix. In other words, the clinical outcomes depend much, if not entirely, on the methods utilized to produce a biologic scaffold material for therapeutic application. The vast majority of biologic scaffolds designed to treat non healing wounds are engineered to degrade. The breakdown of these scaffolds is particularly important for the release of embedded signaling molecules and the generation of cryptic peptide compounds by enzymatic cleavage of parent molecules, such as collagen and laminin. These bioactive cryptic peptides have been found to have a considerable impact on the biological activity of these materials (4;5). The study's objective was to assess the effectiveness of Lyophilized Urinary Bladder Submucosa in the healing of open wounds.

Materials and methods

Sixty mature white rabbits from New Zealand weighing 1 ± 0.300 kg were studied, and all animals shared the same standards of bedding and ambient conditions. They were used and randomly separated into two groups (n = 30), ranging in age from 9 to 12 weeks. One open parallel circular full-thickness (1.5 cm in diameter) skin incision was created on the back of the animals using a punch machine after general anesthesia and animal preparation for aseptic surgery. The rabbits were sorted into two equal groups at random. histopathological specimens were collected at (7, 14, and 21 days after wounding). During the conduct of the study, the national guidelines for the handling and use of laboratory animals were adhered to. The animals were individually restrained and kept in stainless steel cages with plastic covers in typical laboratory conditions (20–24 C and 60% relative humidity), where they also got anti-worm medicine before the experiment. doing clinical and laboratory testing to confirm his disease-free status.

Ethical approval

The High Committee for Review and Approval of Research Proposals of the Faculty of the University of Al-Qadisiyah College of Veterinary Medicine gave its approval to all protocols.

Experimental Design

Group (1) served as a control group for untreated skin wounds. In Group 2, lyophilized bovine UBM was used as a scaffold in the first day following surgery to treat an acute wound, while 2gm of bovine

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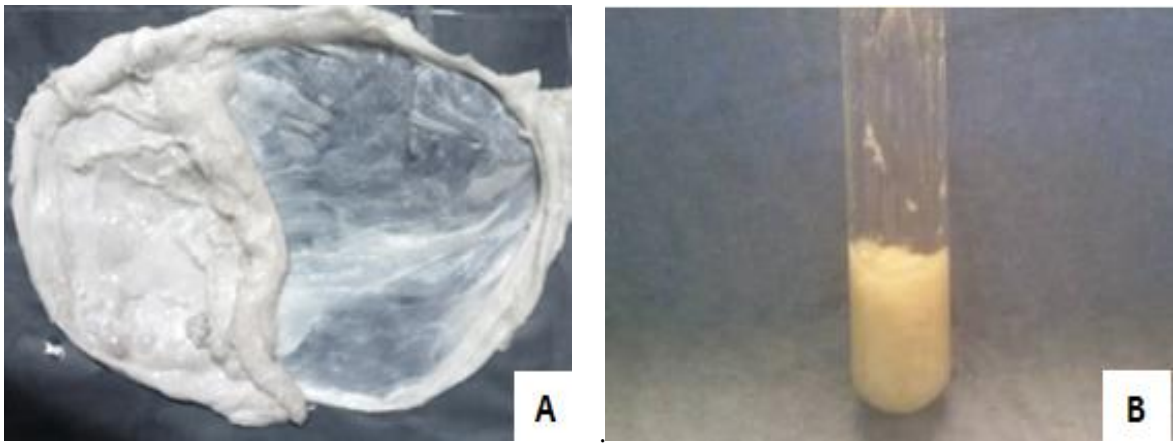
UBM hydrogel was applied topically once daily from the second day following surgery for seven days.

Preparation of Decellularization Bovine Urinary Bladder Matrix: At the nearby butcher shop, fresh urinary bladders from recently slaughtered cows were collected, and UBM-ECM was created as a decellularized scaffold in accordance with (6). In a nutshell, tap water was used to temporarily fill the urinary bladder in order to make it easier to trim and remove the adipose and exterior connective tissues using scissors and then use the tap water to wash it. With a knife scrape, the tunica serosa, tunica muscularis, and the majority of the muscularis mucosa were manually separated from the bladder tissue, resulting in a flat rectangular sheet. By submerging the sheet in a solution of 0.1% peracetic acid (PAA) and 4% ethanol solution on a shaker for two hours, the residual (sub-mucosal layer) was then decellularized and disinfected. The ECM was next rinsed in PBS (pH 7.4), 100 IU/ml penicillin, 100 g/ml streptomycin, and 100 g/ml amphotericin combined at 25 °C with trembling, in two changes of deionized water, and finally in one change of PBS, lasting 15 minutes each. The resulting decellularized ECM scaffolds were then stored at 4 °C for five hours before being terminally sterilized by immersion in PBS containing antibiotics and antifungal medications.

Preparation of Bovine Urinary Bladder Matrix Hydrogel: The urinary bladder submucosa hydrogels was obtained as previously described by (7). The decellularized UBM sheets were moved to -20°C for 24 hours, then to a deep freezer at -80°C for 5 days. The scaffolds were then freeze dried in a freeze dryer (FTS Systems Bulk Freeze Dryer Model 8-54) for lyophilization until they were completely dry, chopped into small sheets for immersion in liquid nitrogen, and reduced to small pieces by a rotary knife mill. The collected powder has been maintained in a sterile container after being sterilized at 60°C in a dry oven for 16 hours. The urinary bladder submucosa hydrogels were made quickly by digesting 100 mg of comminuted UBM in 10 mL of pepsin (Gibco USA) diluted in 0.01 N hydrochloric acid for 48 hours at room temperature. After neutralizing the pre-gel samples to pH 7.4 using 0.1 N NaOH and PBS (10-1), they were incubated for an hour at 37 °C to create hydrogels as in Fig.1A, B.



Figuer.1: Photograph showed the steps of bovine UBM-powder fabrication **A**. Mechanical separation of mucosal and seromuscular layers from the submucosa of bovine urinary bladder. **B**. UBM hydrogel.

Anesthesia of animals: To prevent the animals from pain or moving around during the circular skin incision, general anesthesia was employed together with the pre-medication anesthetic Diazepam 1mol/g IV. Utilizing an intramuscular injection of a combination of xylazine 2% (3 mg/kg B.w.) and ketamine (30 mg/kg B.w.) during the experiment (8).

Surgical Procedure: Following general anesthesia, the animal's back's incision site was prepared for aseptic surgery. These injured rabbits were distributed at random. Into four groups based on their chosen treatment approach. The backs of all of rabbit in all groups were inflicted with a 1.5 cm full thickness circular skin incision. (clipping, shaving, cleaning the region, applying povidine iodine as an antiseptic, and covering the area with gauze soaked in 70% alcohol) on the lateral thoracic side. By using a punch machine, a full-thickness skin incision measuring 1.5 cm in diameter was created. and left the control group untreated us group. Group (2) received treatment for the incision with lyophilized bovine UBM.

Preparation of specimens for histopathological examinations: Specimens of healed skin (wound biopsies) (2 cm^3) were taken at (7,14, and 21) days post wounding (PW) from all animals after anesthesia of animals. The samples were kept in 10% neutral buffered formalin solution, sectioned at a thickness of 5 µm, and stained with hematoxylin and eosin to assess the status of the healing process (S Kim, 2019; Estevao et., al. 2019).

Measurement of wound contraction: Wound contraction at 3^{th},7^{th} , 14^{th} and 21^{th} days post wounding (PW) was calculated as percentage of the reduction in original wound area size by using the following formula: Percentage of wound contraction = (total

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wound size on (day/n) - wound area on day n / wound area on day 0 x 100) as % orginal wound (11, 12).

Statistical analysis: Morphometric data were statistically analyzed, using ANOVA test, and Least Significant Difference (LSD) to find the significance between groups under the level of P<0.05 (13).

Results:

Results from this study were varied. Table -1 displayed the mean ± SE of the diameter values of the wound contraction over the period of the study's 3th day, 7th day, 14th day and 21thday. On the 3th day of the study, the results showed a significant decrease (p ≤ 0.05) in wound diameter in group G2(13) compared with G1(13.90) at the same time. On the 7th day of the study, the results showed a significant decrease (p<0.05) in wound diameter in group G2(11) compared with G1(12) at the same time. At the 14th day, there are significant decrease (p≤ 0.05) in results of wound diameter in group G2(5.5) compared with G1(10) at the same time. On the 21th day of the study, the results showed a significant decrease (p≤ 0.05) in wound diameter in group G2(2.53), compared with G1(4.93) at the same time.

Table (1): mean ± SE of the diameter values of the wound contraction recorded in experimental rabbets.

Groups	Diameters of the wound (mm)				
	0 day	3th day	7th day	14th day	21thday
G1 (n=30)	15±0Aa	13.90±0.21Ab	12±**0.18Ac**	10±0.29Ad	4.93±0.19Ae
G2 (n=30)	15±0Aa	13±0.22Bb	11±0.21Bc	5.5±0.20Bd	2.53±0.09Be

* LSD $_{0.05}$ = 0.408

Macroscopic appearance: Dryness and darkening wounds of G1, G2, appeared on the third day. The G1, G2 wounds were dry and black at day 7, and the diameters had clearly shrunk. A little amount of proliferation tissue began to grow at day 14 and the diameter of G1 cells continued to shrink, while G2 cells continued to grow proliferation tissue to the point where it nearly filled the wound site. All groups had noticeable scar tissue formation by day 21 as in Fig.-2.

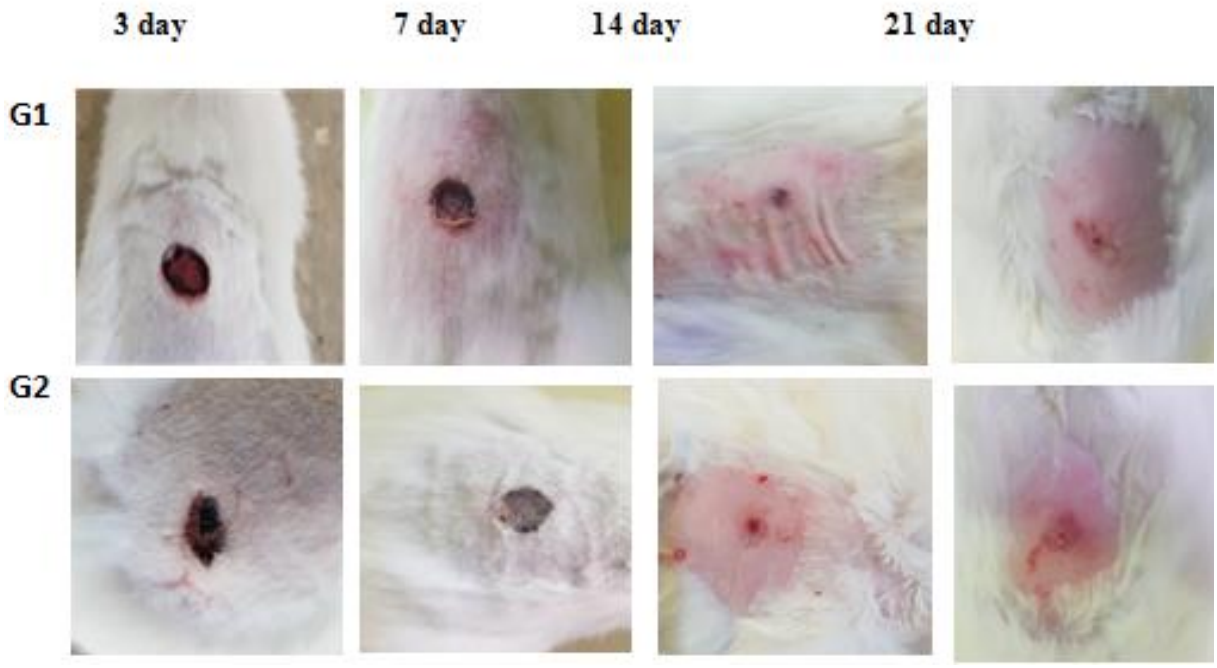

Figure -2: Morphological appearance of wounds of all groups at different periods.

Histopathological assessment of the wound healing: G1 at the 7-day showed partial healing in the epidermal layers, which seemed to be split and had modest hyperplasia on each side of the injury. Pus formed above the epidermis which contains dead neutrophils and tissue debris. The dermis had abundant granulation tissue and the growth of tiny new blood vessels, along with the infiltration of inflammatory cells, primarily macrophages as in Fig. 3. G2 at 7th days showed higher magnification a scab showed attached closely with thin layers of epidermis. Granulation tissue is profuse and formation of small and new hair follicle in the site of injury as in Fig. 4. G1 at 14th days showed high infiltration of inflammatory cells mainly macrophages

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(P-ISSN 1818-5746/ E-ISSN 2313-4429)
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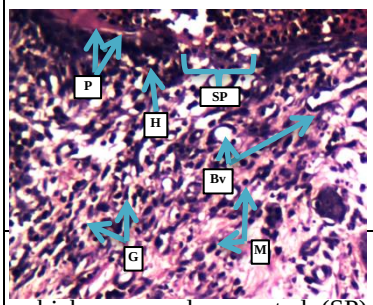
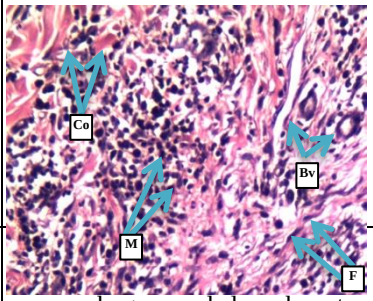
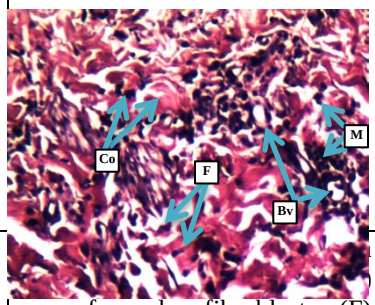
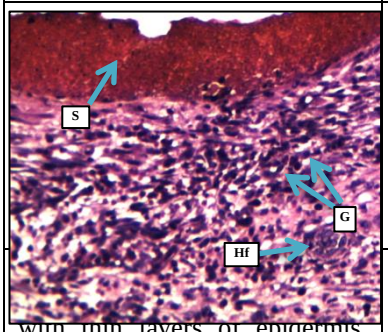
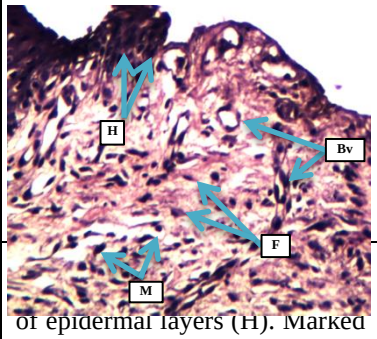
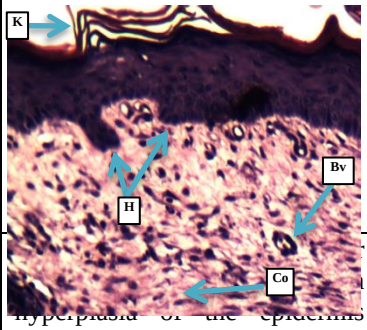
and lymphocytes with small and new blood vessels vertically on the proliferation of fibroblasts with fine network of collagen in the site of injury as in Fig. 5. G2 at 14th days showed Complete sloughing and absence of scab and hyperplasia of epidermal layers. Marked new blood vessels which showed vertically on the site of wound and profuse fibrosis due to proliferation of fibroblast, and scattered macrophages and lymphocytes as in Fig. 6. G1 at 21th days showed new vascularization in which new blood vessels are formed, fibroblast proliferation which produce the collagen that replaces the site of injury. Macrophage infiltration also are seen.as in Fig. 7. G2 at 21th days showed marked keratinized layer over the epidermis with hyperplasia of the epidermis mainly the stratum basale. New blood vessels and regular arrangement of collagen in the site of wound as in Fig. 8.

	7th	14th	21th
G1	 which appeared separated (SP) with mild hyperplasia in the both edges of the injury(H). Pus (P) formed above the epidermis which contains dead neutrophils and tissue debris. Granulation tissue (G) showed profuse in the dermis and formation of small new blood vessels (Bv), with infiltration inflammatory cells mainly macrophages(M). 50X H&E	 macrophages and lymphocytes (M) with small and new blood vessels (Bv) vertically on the proliferation of fibroblasts (F) with fine network of collagen (Co) in the site of injury. 50X H&E.	 are formed, fibroblast (F) proliferation which produce the collagen (Co) that replaces the site of injury. Macrophage (M) infiltration also is seen.50X H&E.
G2	 with thin layers of epidermis. Granulation tissue (G) is profuse and formation of small and new hair follicle (Hf) in the site of wound. 50X H&E.	 of epidermal layers (H). Marked new blood vessels (Bv) which showed vertically on the site of wound and profuse fibrosis (F) due to proliferation of fibroblast, and scattered macrophages and lymphocytes (M). 50 X H&E.	 hyperplasia of the epidermis mainly the stratum basale (H).New blood vessels (Bv) and regular arrangement of collagen (Co) in the site of wound.50 X H&E.

Discussion:

The objectives of this study were to assess the effect of lyophilized bovine urinary bladder submucosa on rabbit full thickness skin wound healing, the effectiveness of lyophilized bovine urinary bladder submucosa. In this study, rabbits were used because they were small animals, widely bred, inexpensive against the price of larger animals, and had short life cycles (gestation, lactation, and puberty). Rabbits were also very docile and non-aggressive, making them easy to handle and observed (14). UBM-ECM: It was

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discovered that ECM components such collagen, glycosaminoglycans, vitronectin, and laminin were superior at acting as natural therapeutic agents (15). Cells participating in the healing process are influenced by cytokines, growth factors, and interactions with ECM components via integrin, receptors, and sticky molecules as damaged matrix components are removed by neutrophil and macrophage proteases, the original scar tissue is remodeled., matrix metalloproteinases generated by endothelial cells and fibroblasts allow these cells to migrate (16). Also, in my perspective, it totally covered the wound and stopped any microbial invasion.

Macroscopic Findings: The wound diameters in the treated groups showed significant decreases, and there was no inflammation or infection during the observation period, pointing to the major advantages of the UBM treatment , in my opinion this means the treatment stimulated growth Fibroblast as well as stimulating formation of collagen III to be scaffold grow on it Fibroblast as growth progresses, granulation tissue forms in a wave-like shape that starts from the edges of the wound gap towards the center, and over time the collagen type III fibers transform into collagen type I. In the control groups, such wound size reductions take a lot of time. G1at 7th displayed redness, and the wound's diameter was the same as when it was first created because fibroblast did not still grow. G2 at 7th showed a clear shrinking of the wound's size and width because UBM treatment had a significant role in its contraction and moistening Compared to G1, this agree with (17) who shown that healing occurs more quickly in humid environments than in dry ones because humidity reduces cell desiccation, enhances cell migration, stimulates angiogenesis, increases collagen synthesis, and improves intercellular communication, All of these factors would translate into clinical effects such as decreased pain, heat, insulation autolytic debridement, increased healing speed, and better scar quality. Additionally, there would be no redness and the wound would be smaller than G1, and there would be no inflammation or pus because of the anti-inflammatory and anti-microbial effects of the treatments. The results agreed with (18). Light redness was present on G1 at 14th day , and the wound's diameter was less. In contrast to G1, the wound in G2 at 14th day clearly narrowed more over the course of seven days, and this was due to the important role that UBM treatment played in promoting wound contraction and protecting the skin. Additionally, there was no redness and the wound shrank more than in G1, and there was no inflammation or pus because UBM had an anti-inflammatory and anti-microbial effect. As recorded by (19 ; 20). G1 at 21th day showed nearly reduction in diameter of the wound and scar tissue formation was visible clearly. These results were due to G1 left with no any treatment. G2 at 21th day showed slight healing and little scar tissue. These results were due to the efficacy of UBM constituents on angiogenesis process. By promoting the expression of TGF-1, VEGF, MMP-9, and type I collagen, UBM displays noticeably increased activity for rapid endogenous cell ingrowth and creates a more pronounced pro-regenerative and pro-remodeling milieu. Overall, our findings imply that UBM has a strong bioactivity that is intrinsic for in situ tissue regeneration. Results were agree of (21).

Microscopic Findings: G1 at 7th day showed In both edges of the injury, there was inadequate healing in the epidermal layers, which appeared separated with modest hyperplasia. Pus formed above the epidermis which contains dead neutrophils and tissue debris. Granulation tissue showed profuse in the dermis and formation of small new blood vessels, with infiltration inflammatory cells agree with (22). A scab forms which covering over a site of healing. This scab appeared fractured and fragmented. Also, there was pus present between the scab and the epidermis. There was mild hyperplasia of the epidermal layers agree with (23; 24). G2 at 7th day showed a scab appeared sticks very hard with the epidermis. The epidermis is showed very thin and mild hyperplasia in the two edges of skin wound, Profuse granulation tissue which appeared along the dermis layer in the wound area, and formation of small blood vessels. Few of collagen was seen as well, formation of small and new hair follicle in the site of wound, (21) found by increasing the expression of TGF-1, VEGF, and type I collagen, UBM displays noticeably improved activity for rapid endogenous cell ingrowth and creates a more pronounced pro-regenerative and pro-remodeling microenvironment. Overall, our findings imply that UBM has a strong bioactivity for in situ tissue regeneration by nature. Also showed infiltration of inflammatory cells mainly macrophages and lymphocytes and fibrosis on the site of wound accompanied with (25). In the current study the G1 at 14th day showed the presence of moderate granulation tissue caused the rate of re-epithelialization to slow down, which in turn caused the wound size to not contract clearly. These findings were in accordance with (26). Histological analysis of the G2 UBM-treated groups' wounds at 14th day showed marked downward proliferation of the epidermis's basal layer. In the dermis, there was extensive fibrosis brought on by fibroblast proliferation, as well as sporadic macrophages, lymphocytes, and collagen that replace the location of the wound and generate new vascularization and blood vessel development with regularly spaced-out collagen fibers. This result was consistent with that of (27) who reported that through promoting progenitor cell infiltration, adhesion, and proliferation in conjunction with accelerating angiogenesis at the wound site, as well as by enhancing the formation of granulation tissue and depositing host-derived neomatrix (collagen contents), implanted ECM demonstrated tissue healing. A small scab which showed over the site of injury in G1 at 21th day. The tow edges of skin wound appear almost bound together

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due to the hyperplasia of epidermal layers. In the dermis, fine of collagen fibers replaces the damaged tissue with scattered inflammatory cells mainly macrophages, and formation of new vascularization, results accompanied with (28). New vascularization in which new blood vessels are formed, fibroblast proliferation which produce the collagen that replaces the site of injury. macrophage infiltration (29). In G2 at 21th day formation of keratinized layer over the epidermis. The epidermal layers showed hyperplastic and the two edges of skin wound showed connected together. In the dermis regular arrangement of fibrosis and collagen network with newly formed blood vessels. new and small hair follicles also are seen in the sit of wound due to the efficacy of UBM constituents which agree with (18; 30).

Conclusion

The treatments of open skin wounds with lyophilized bovine UBM improve the wound healing.

Conflict of interest

No conflict was declared for this study.

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