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The therapeutic effect of endoform on cutaneous wounds healing in experimentally induced diabetic dogs

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Abstract

This research was planned to evaluate the efficacy of Endoform to heal cutaneous wounds in experimentally induced diabetic dogs. Eighteen adult female dogs were utilized. The animals were divided into three groups. The animals were injected with alloxan at 50 mg/kg. in the second and third groups to induce diabetes, while in the first group, the animals were not injected with alloxan. A total thickness skin wound about 2cm in diameter was established on animals' lateral aspects of the forelimbs. In the first and second groups, the skin wounds were not treated, whereas in the third group, the skin wounds were treated with topical dressing of Endoform. The gross and histopathological study with statistical analysis for histopathological scoring at 7,14, and 21 days post-wounding depended on the analysis of the obtained results. Grossly, the wounds in the first and third animal groups usually healed. While in the second animals' group, the wounds didn't heal and suffered from necrosis. In all groups, the histopathological results revealed granulation tissue formation, the presence of inflammatory cells, the formation of new blood vessels, and re-epithelialization. The degree of wound reepithelization in the second group appeared slower than in the first and third groups, in addition to severe infiltration of inflammatory cells with the persistence of granulation tissue development. In conclusion, we could use Endoform to accelerate the process of cutaneous wound healing in diabetic dogs.

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Introduction

The wound is a damage or break in the continuity of body tissues. The skin wounds are formed by several causes, such as trauma, and thermal and surgical injuries (1-3). Accurately treating wounds by cleaning, debridement, and dressing is imperative for avoiding complications such as infections and delayed healing (4). The materials used to dress the cutaneous wounds should have some characteristics such as non-toxic, antibacterial activity, less cost, adherence, and biocompatibility (5). The healing process of the wounds occurs immediately after tissue injury through a series of events. Generally, these wound healing events include the repair and maturation phases (6-9). The large wounds may not heal by primary intention due to excessive tissue loss, infection with microorganisms, and loss of connection between wound edges (10). Therefore, not all skin wounds heal properly by primary intention, as in large full-thickness skin wounds that are healed by secondary intention (11-13). Also, several factors may interfere with wound healing, causing delayed healing. These are local factors, such as oxygenation, foreign bodies, infection, systemic stress conditions, nutrition, diabetes, obesity, and some medications (14,15). In dogs, diabetes mellitus (D.M.) is considered a more common endocrine disease characterized by hyperglycemia, loss of body weight, and glucosuria (16).

Generally, D.M. is classified mainly into types 1 and 2. In D.M. type 1, there is an absolute deficiency of insulin because of the disease related to immune-mediated beta cell destruction. In D.M. type 2, the disease is characterized by impaired insulin with insulin resistance. Other types of D.M. arise from other causes, such as diseases of the pancreas, and endocrinopathies, such as hyperadrenocorticism and hypersomatotropism (17). The D.M. rate is higher in female dogs than males (18). D.M. causes impairment in the healing process of acute wounds and leads to the development of chronic nonhealing wounds, for example, forms of foot ulcers, which appear as a complication of diabetes (19). Numerous methods are available to induce diabetes in experimental animals; alloxan is one of the most diabetogenic agents (20). Several types of non-medicated, medicated, passive, bioactive, and interactive dressings, and materials, such as hydrogel, hyaluronic acid, chitosan, and aloe vera gel, have been used for the treatment of nonhealing wounds (21). Passive dressings are utilized to cover the wound bed and to allow healing only (22). Endoform® is a unique extracellular matrix (ECM), derived from the ovine forestomach. It is planned for all phases of wound healing to correct and organize tissue in acute and chronic wounds. The composition of Endoform® provides a biological, porous structure for fast infiltration of cells such as epithelium and fibroblast to enhance the wound healing process (23-25). Generally, two types of Endofrom are present: natural or antimicrobial bio-scaffold (23).

Therefore, the study aims to assess the effectiveness of Endoform® as a dressing subject to repair skin wounds in diabetic dogs.

Materials and methods

Ethical approve

The study was ratified by the Ethics Committee of the Faculty of the Veterinary Medicine College, Mosul University. No. U.M.VET.2023.004.

Experimental animals

Eighteen adult female dogs were used. The animals aged between 1-2 years and weight of 25±1.8 kg. The animals were divided into three equal groups. All animals blood sugar levels were measured to ensure they were not originally diabetic and preserved in cages in the animal house of Veterinary Medicine College, Mosul University.

Experimental design

The total experimental animals used in this work were eighteen adult female dogs. The blood sugar level of all animals was measured before establishing a skin wound through a glucometer to record the normal blood sugar of each animal. The animals were divided into three equal groups. The animals of the second and third groups were injected intravenously with alloxan at a dose of 50 mg/kg. after fasting the animals for 24 hours (26). The injected animals with alloxan received 5% glucose solution intravenously to prevent hypoglycemia. The injected dogs with alloxan were examined once every three days during the study by using a glucometer to confirm the accuracy of diabetes and to ensure the animals didn't return to normal state. All second and third group animals became diabetic after three days. 2 cm. A thick skin wound was created on the lateral side of the fore limb in all experimental animals after induction of anesthesia through injection of ketamine and xylazine combination at a dose of 10 mg/kg and 2mg/kg intramuscularly, respectively. The induced skin wounds of the first group of animals were not treated as a negative control group (nontreated – nondiabetic (G^-)). The induced skin wounds of the second group animals did not also repair as a control positive group (nontreated – diabetic (G^+)), while the skin wounds of the third group animals were treated with local application of Endoform® (Aroa Biosurgery Ltd, New Zealand, 2018) (Figure 1) as a treated group (treated – diabetic (T.G.).

Figure 1: shows Endoform®.

Surgical procedure

After induced diabetes for the group 2 and 3 animals, a full-thickness square shape 2x2 cm skin wound was created on the lateral aspect of the fore limb in all experimental animals under general anesthesia (Figure 2). In the first and second groups, the skin wounds were not treated; only washed with normal saline daily with dressing. At the same time, the skin wounds of the third group were treated by local application of Endoform® directly after wounding (Figure 3). The re-application of the Endoform® piece was accomplished after 3 days. All experimental animals were injected with penicillin-streptomycin (1ml/10 kg.) (penicillin 200000 I.U. + streptomycin 200mg / 1 ml, Interchemi-Holand).

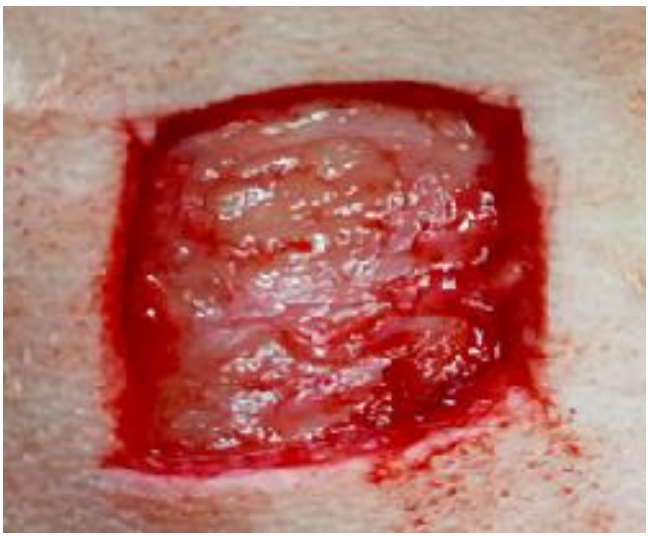

Figure 2: shows induced skin wounds for all experimental animals.

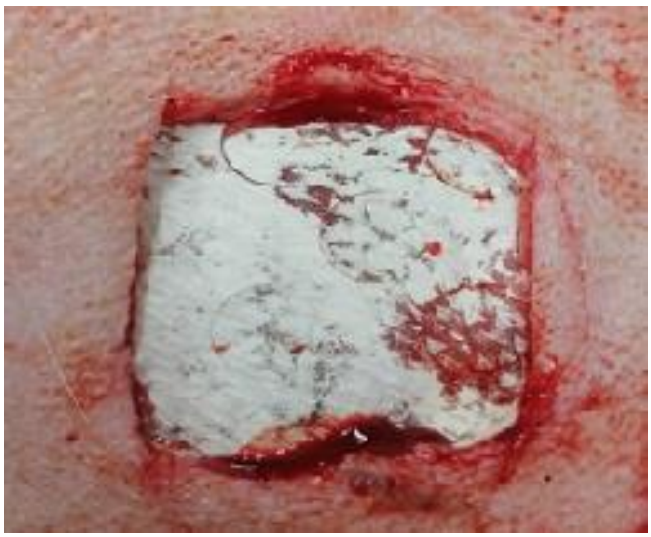

Figure 3: shows Endoform® on skin wound for the group 3 only.

Assessment of wound healing

The study's evaluation was based on monitoring gross changes in skin wounds healing postoperatively and studying histopathological changes 7,14, and d 21 days postoperatively with statistical analysis of histopathological scores. The scoring of histopathological sections included the following criteria; [1] Intensity of granulation tissue, [2] Intensity of new blood vessel formation (angiogenesis), [3] Intensity of inflammatory reaction, and [4] Intensity of re-epithelialization (Table 1).

Statistical anaylsis

The data of histopathological descriptive scores of the granulation tissue, angiogenesis, severity of the inflammatory response and re-epithelialization were done by a pathologist and analyzed statistically by Kruskal-Walli's test and used Pairwise Multiple Comparison Procedures (Tukey Test) at $P \leq 0.05$. The Sigma Plot (version 12.5) software program analyzed the data for statistical analysis.

Table 1: Scoring of histopathological sections (27)

Criteria	0	1	2	3
G.T.	Absent	Discrete	Moderate	Intense
Degree of angiogenesis	Absent	Discrete	Moderate	Intense
Inflammatory reaction	Sever	Moderate	Few	Absent
Re-epithelialization	Absent	Discrete	Moderate	Intense

Results

Gross changes

The gross changes in skin wounds of the first group during all the study periods showed obvious alternations in the wound shape and size. The wounds healed normally and were closed completely by new connective tissue and re-epithelialization with reduced size (Figures 4-6).

In the second group, the skin wounds of the diabetic animals were characterized by impairment in the healing process compared with the skin wounds of the first group animals. The wounds showed a delayed reduction in their size, with some areas of necrosis and discoloration of the wound bed at the end of the study (Figures 7-9).

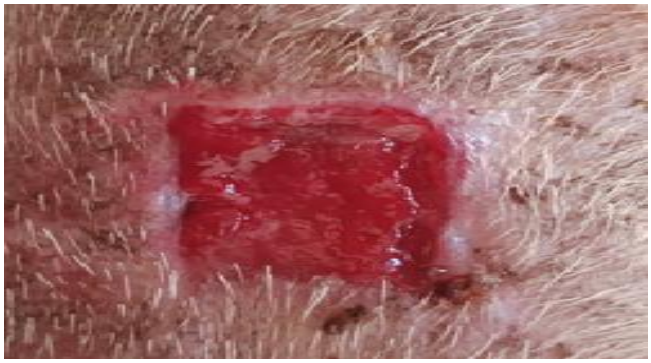

Figure 4: shows the shape and size of the skin wound in the first group on day 7.

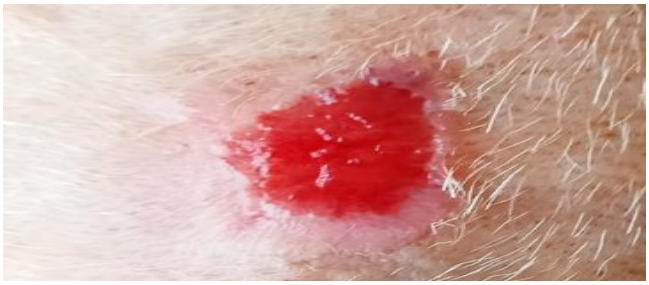

Figure 5: shows the shape and size of the skin wound in the first group on day 14.

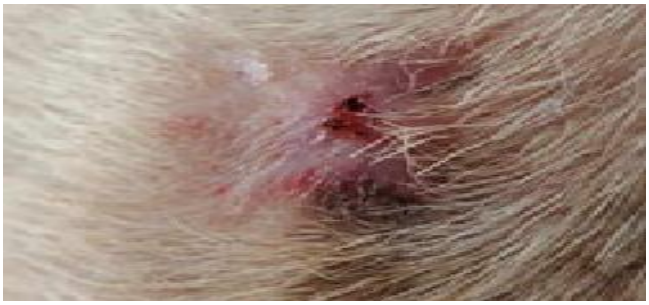

Figure 6: shows the shape and size of the skin wound in the first group on day 21.

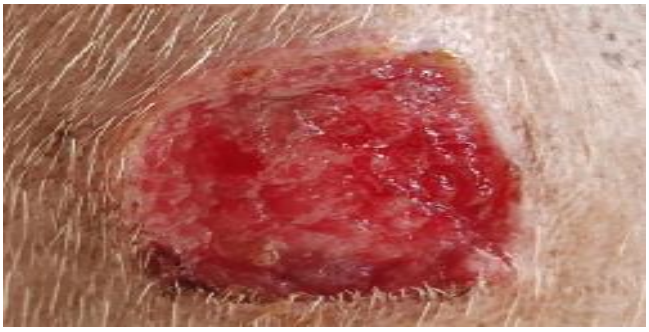

Figure 7: shows the shape and size of the skin wound in the second group on day 7.

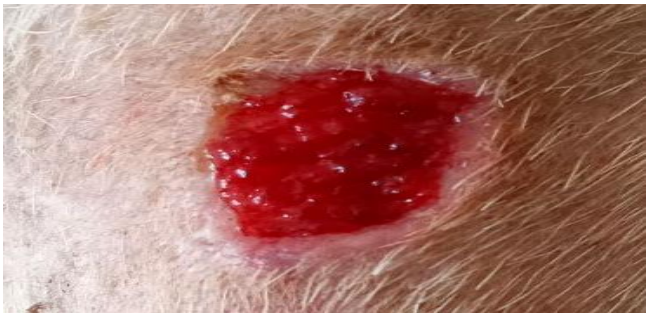

Figure 8: shows the shape and size of the skin wound in the second group on day 14.

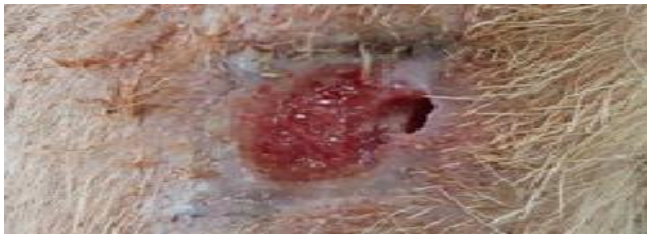

Figure 9: shows the shape and size of the skin wound in the second group on day 21.

In the third group, the gross changes of skin wounds decreased in size and healed completely, although the animals in this group suffered from diabetes (Figures 10-12). The wounds disappeared utterly.

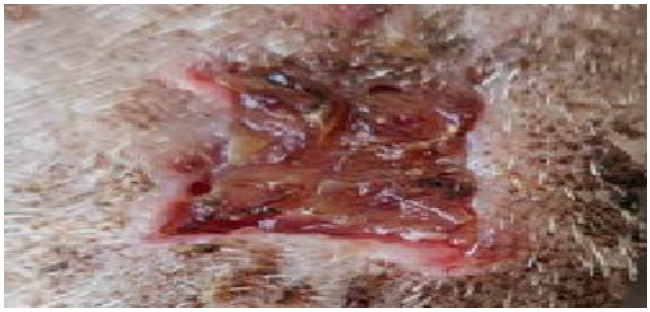

Figure 10: shows the shape and size of the skin wound in the third group on day 7.

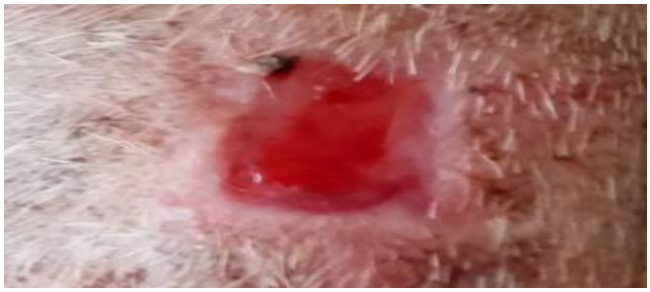

Figure 11: shows the shape and size of the skin wound in the third group on day 14.

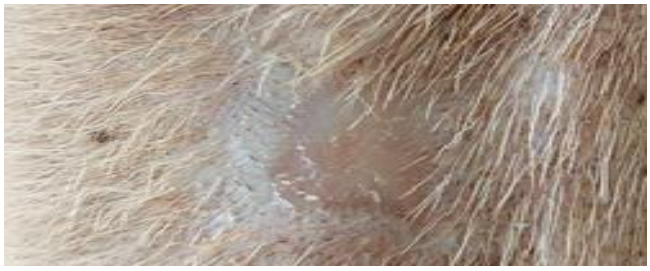

Figure 12: shows the shape and size of the skin wound in the third group on day 21.

Histopathological findings

The histopathological features at the skin wound site after 7 days of wound induction of the first group were characterized by new formation of granulation tissue and blood vessels with inflammatory cells (Figure 13). At 14 days post-wounding, the changes at the skin wound site were represented by the features shown in the previous period with the beginning of the re-epithelialization process (Figures 14 and 15). At 21 days post-wounding, the site of the wound was characterized by progress in the degree of re-epithelialization without the presence of inflammatory cells. Granulation tissue and angiogenesis were also shown (Figure 16).

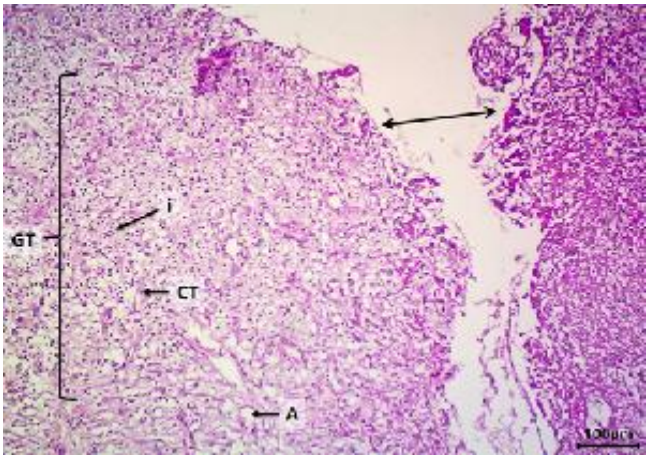

Figure 13: Histopathological section in the first group after 7 days at the site of the wound (↔) showing the formation of granulation tissue (G.T.), angiogenesis (A), and inflammatory cells (i) (H&E, 10X).

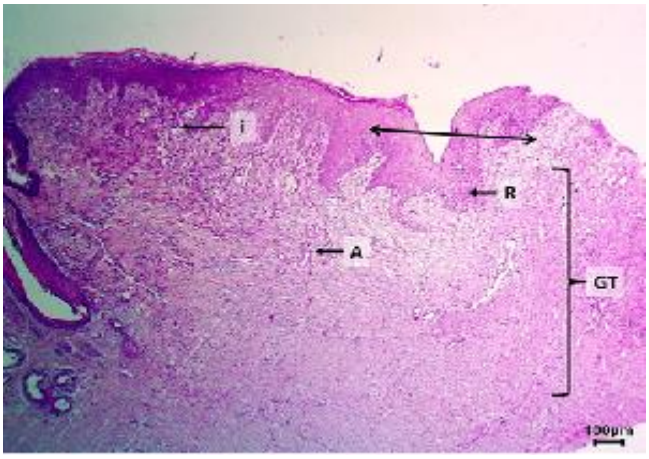

Figure 14: Histopathological section in the first group after 14 days at the site of the wound (↔) showing granulation tissue (G.T.), angiogenesis (A), inflammatory cells (i), and re-epithelialization (R) (H&E, 4X).

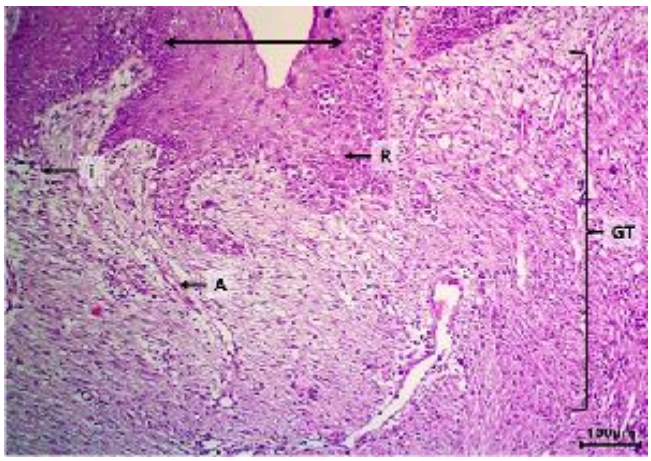

Figure 15: Histopathological section in the first group after 14 days at the site of the wound (↔) showing granulation tissue (G.T.), angiogenesis (A), inflammatory cells (i), and re-epithelialization (R) (H&E, 10X).

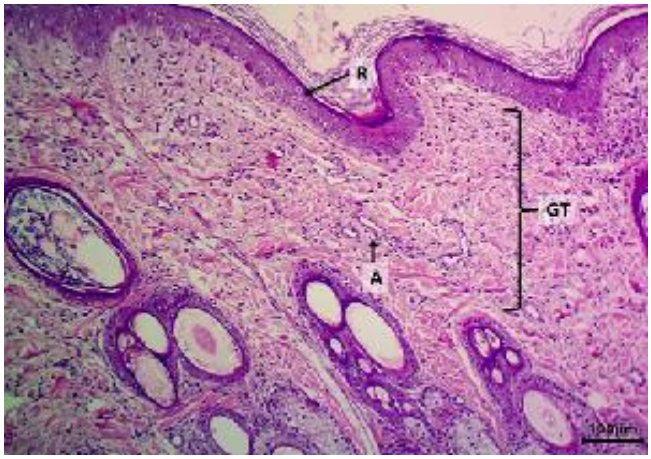

Figure 16: Histopathological section in the first group after 21 days at the site of the wound (↔) showing granulation tissue (G.T.), angiogenesis (A), and complete re-epithelialization (R) (H&E, 10X)

In the second group, the histopathological changes after 7 and 14 days of wound induction were represented by the development of new granulation tissue, the presence of high inflammatory cell infiltration, the formation of new blood vessels, and some areas of tissue necrosis without the occurrence of re-epithelialization (Figures 17-19). At 21 days post-wounding, the wound site was characterized by the beginning of re-epithelialization with granulation tissue, inflammatory cells, and angiogenesis (Figure 20).

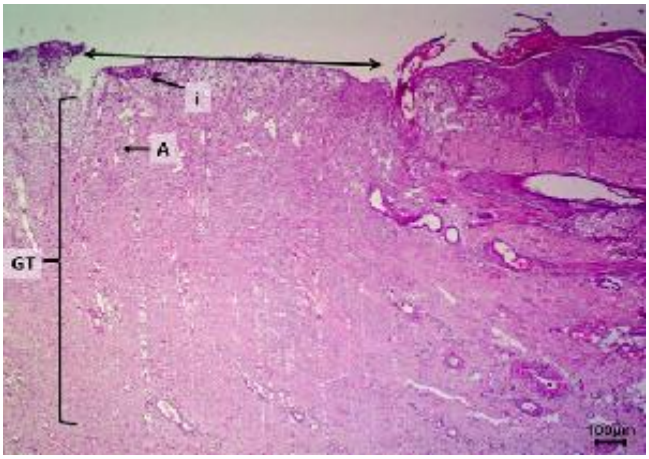

Figure 17: Histopathological section in the second group after 7 days at the site of the wound (↔) showing the formation of granulation tissue (G.T.), angiogenesis (A), and inflammatory cells (i) without re-epithelialization (H&E, 4X).

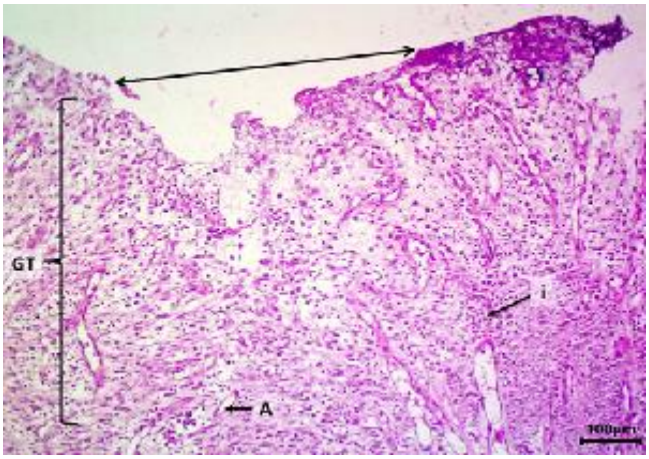

Figure 18: Histopathological section in the second group after 7 days at the site of the wound (↔) showing the formation of granulation tissue (G.T.), angiogenesis (A), and inflammatory cells (i) without re-epithelialization (H&E, 10X).

In the third group, the histopathological results at the site of the skin wound post 7 of wound induction were represented by the development of new blood vessels with granulation tissue, inflammatory cells, and re-epithelialization (Figure 21). At 14 days post-wounding, the wound site was characterized by degree of re-epithelialization with granulation tissue, inflammatory cells, and angiogenesis (Figures 22 and 23). At 21 days, the histopathological sections revealed a complete degree of re-epithelialization relatively without granulation tissue and inflammatory cells (Figure 24).

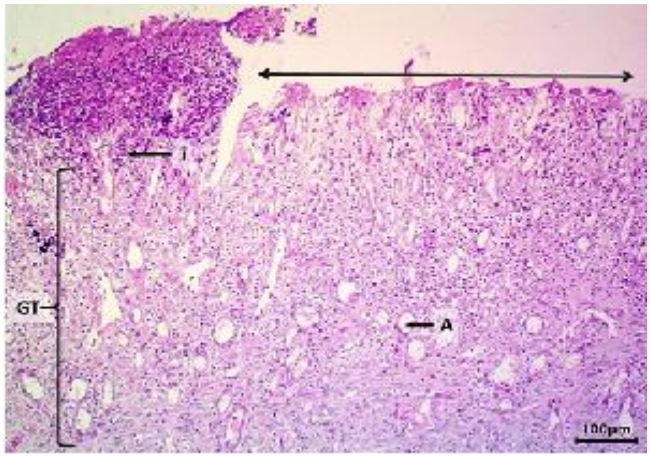

Figure 19: Histopathological section in the second group after 14 days at the site of the wound (↔) showing granulation tissue (G.T.), angiogenesis (A), and inflammatory cells (i) (H&E, 10X).

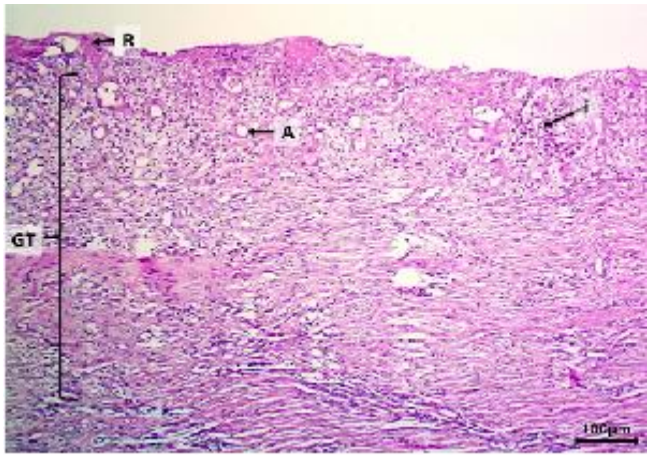

Figure 20: Histopathological section in the second group after 21 days at the site of wound showing granulation tissue (G.T.), angiogenesis (A), inflammatory cells (i), and re-epithelialization (R) (H&E, 4X).

Scoring analysis

The intensity of granulation tissue and degree of inflammation was characterized by disappearance at the final period of the study in the first and third groups, unlike the second group, where the results of statistical analysis of granulation tissue and inflammation scoring showed a significant difference at $P \leq 0.05$ in the first and third group when compared with the second group (Tables 2 and 3). In addition, a low degree of angiogenesis and re-epithelialization appeared in the second group at $P \leq 0.05$ during the study period compared to other groups (Tables 4 and 5).

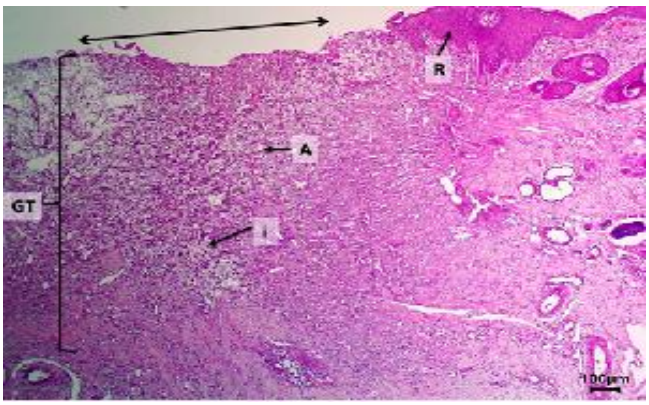

Figure 21: Histopathological section in the third group after 7 days at the site of the wound (↔) showing the formation of granulation tissue (G.T.), angiogenesis (A), inflammatory cells (i), and re-epithelialization (R) (H&E, 4X).

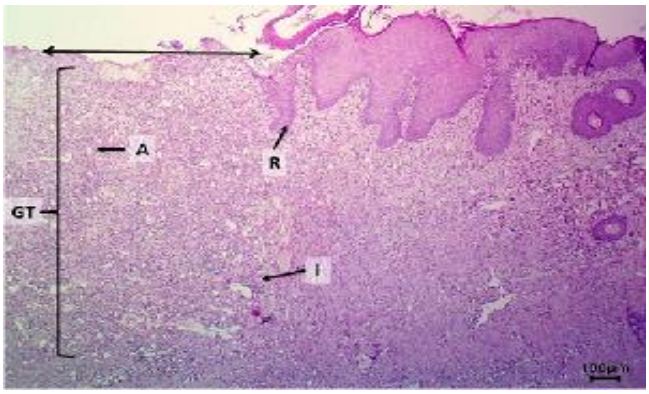

Figure 22: Histopathological section in the third group after 14 days at the site of the wound (↔) showing granulation tissue (G.T.), angiogenesis (A), inflammatory cells (i), and re-epithelialization (R) (H&E, 4X).

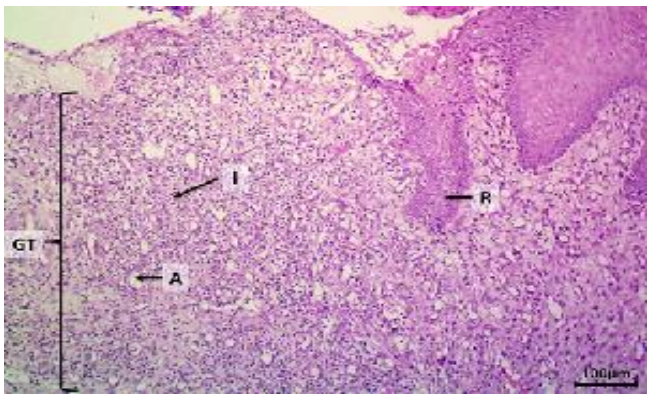

Figure 23: Histopathological section in the third group after 14 days at the site of the wound (↔) showing granulation tissue (G.T.), angiogenesis (A), inflammatory cells (i), and re-epithelialization (R) (H&E, 10X).

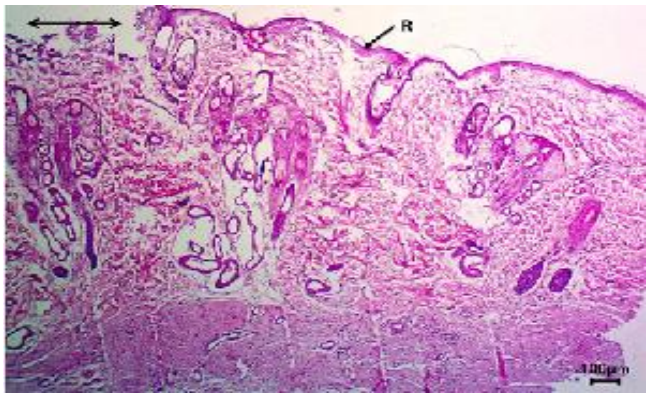

Figure 24: Histopathological section in the third group after 21 days at the site of the wound (↔) showing re-epithelialization (R) without granulation tissue, and inflammatory cells (H&E, 4X).

Table 2: Scores of the granulation tissue for all groups at all periods

Groups	7 days Median (IQR)	14 days Median (IQR)	21 days Median (IQR)	*P*-value
First group	3(2) Aa	2(2) Aab	1(1) Ab	0.045
Second group	2(2) Aa	2(2) Aa	2(1) Aa	0.511
Third group	3(2) Aa	2(2) Aab	0(0) Bb	0.048
P-value	0.439	0. 829	0.045	

Different capital and small letters mean significant differences among groups and periods, respectively, at P≤0.05.

Table 3: Scores of the inflammatory cells for all groups at all periods

Groups	7 days Median (IQR)	14 days Median (IQR)	21 days Median (IQR)	*P*-value
First group	2(2) Aa	1(1) Aab	0(1) Ab	0.035
Second group	3(2) Aa	3(3) Aa	2(1) Aa	0.711
Third group	1(1) Ba	1(0) Bab	0(0) Bb	0.439
P-value	0.048	0.029	0.025	

Different capital and small letters mean significant differences among groups and periods, respectively, at P≤0.05.

Table 4: Scores of the Angiogenesis for all groups at all periods

Groups	7 days Median (IQR)	14 days Median (IQR)	21 days Median (IQR)	*P*-value
First group	2(1) Aa	2(2) Aa	1(1) Aa	0.511
Second group	1(1) Ab	3(2) Aa	2(2) Aab	0.045
Third group	2(2) Aab	3(2) Aa	1(0) Ab	0.042
P-value	0.439	0. 829	0.086	

Different capital and small letters mean significant differences among groups and periods, respectively, at P≤0.05.

Table 5: Scores of the re-epithelialization for all groups at all periods

Groups	7 days Median (IQR)	14 days Median (IQR)	21 days Median (IQR)	*P*-value
First group	0(0) Ab	3(2) Aa	4(2) Aa	0.029
Second group	0(0) Aa	1(1) Ba	1(1) Ba	0.829
Third group	1(1) Ab	2(1) Aa	3(3) Aa	0.045
P-value	0.139	0.045	0.025	

Different capital and small letters mean significant differences among groups and periods, respectively, at P≤0.05.

Discussion

The stages of wound healing are a series of events that evoke some mediators to facilitate wound healing, such as growth factors and cytokines (28-31). In the first group, the healing process of skin wounds was accomplished within normal range without any complications, where the wounds healed completely through newly granulated tissue and the process of re-epithelialization at the end of the study. The extracellular matrix of the wound bed converts into granulation tissue through a series of events evoked by activated macrophages within a few days post-injury of healthy tissue (6,7). This extracellular matrix acts as a scaffold to migrate fibroblasts and endothelial cells, which allows for the occurrence of angiogenesis and fibroplasia. Also, in this group, the healing process didn't suffer from problems like the second group because of good tissue vascular microcirculation. The process of angiogenesis plays a significant role in the rate of wound healing, where the formation of new blood vessels provides the demand tissues of the wound with nutrition and oxygen (32,33).

In this work, the healing of skin wounds was impaired in the second group, unlike the first and third animal groups, due to the effect of diabetes on the healing process (34,35), where the wounds appeared necrotic with the status of delayed healing. The diabetes leads to some pathophysiological sequelae that affect the vascular, and biochemical components of the tissue (36,37). The hyperglycemia due to diabetes causes hypoxia of tissues (38). This reduction in tissue oxygenation, causes slower vascular circulation and dysfunction of angiogenesis. Also, the degree of skin damage and ulceration was increased in diabetes. In addition, the destruction of tissues and decreased tissue healing were increased also in diabetes due to high levels of protease activity (39). The low degree of re-epithelialization and angiogenesis with more presence of inflammatory cells were shown in the histopathological sections of this group when compared with other groups, and this is due to the effect of diabetes on the microcirculation of the tissue, the diabetes disease, several dysregulations of cellular functions such as cell immunity, phagocytosis, chemotaxis of leukocyte, fibroblasts and epidermal cells proliferation were involved (40). Also, the wounds became more susceptible to infection in diabetes disease because of the high levels of glucose in the bloodstream, which are responsible for decreasing the migration of leukocytes into the tissue of the wound (36). Additionally, a low level of vascular endothelial growth factors in wounds was noticed in the diabetic state (19).

In the third group, the skin wounds healed within normal range, like the first group, although the animals in this group suffered from diabetes. This effect is due to the efficiency of Endoform, which aids in healing wounds without any complications and regrades a suitable synthetic extracellular matrix to repair and enhance acute and chronic wound healing (23). In addition, the histopathological section in this group revealed complete re-epithelialization with the absence of inflammatory cells and the formation of granulation tissues at the final stage of the study, which indicated the excellent and complete healing of induced wounds. This effect belonged to the composition of Endoform, which provides a biological, porous structure for rapid infiltration of epithelium and fibroblast to enhance the wound healing process (23,24). The re-epithelialization appeared very quickly in this group rather than in other groups due to the ability of Endoform, which acts as a scaffold for migrating keratinocytes and covering the bed of wounds. However, the wounds suffered from skin loss and the animal's status of diabetes, where the migration of keratinocytes occurs very fast in partial thickness wounds than in a full-thickness wound where the process of reepithelization cannot progress until the bed of wound

filling with granulation tissue (6,7,33). The less infiltration of inflammatory cells in this group with the absence of inflammatory cells at the end of the study due to the ability of Endoform, which acts as a barrier to protect and cover the wounds from the external environment and the chance of infection where the diabetic wounds more susceptible to infection (36), in addition, the type of Endoform in this research from the antimicrobial type which contains ionic sliver that prevents the colonization of bacteria (41). Also, the presence of Endoform leads to resolving the inflammation with a decreased and rebalanced level of protease that's increased in chronic or open wounds (23). The process of angiogenesis in this group didn't interfere with the healing process, although the animals suffered from diabetes. Moreover, this result is also because of the efficiency of Endoform, which contains many extracellular proteins essential for wound healing, in addition; this product also contains vascular channels to support the establishment of new vasculature (42,43). However, over time, the Endoform was remodeled completely as new tissue (25,44).

Conclusions

Endoform could be used to treat cutaneous wounds in diabetic dogs due to its ability to improve and enhance the healing process of wounds under pathological conditions, such as diabetes mellitus.

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Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

Editorial board note

Muneer S. Al-Badrany and Dhafer M. Aziz the editors of the Iraqi Journal of Veterinary Sciences, did not participate in any stage of the decision-making process for this article.

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التأثير العلاجي للاندوفورم على التئام الجروح الجلدية في الكلاب المصابة بمرض السكري المستحدث تجريبيا

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الخلاصة

صمم هذا البحث لتقييم كفاءة الاندوفورم على التئام الجروح الجلدية في الكلاب المصابة بمرض السكري المستحدث تجريبيا. ثمانية عشر من إناث الكلاب البالغة تم استخدامها حيث قسمت الى ثلاث مجاميع. تم حقن مادة الألوكسان وبجرعة ٥٠ ملغم / كلغم في حيوانات المجموعة الثانية والثالثة لإحداث داء السكري في حين لم تحقن مادة الألوكسان في حيوانات المجموعة الأولى. تم إحداث جرح جلدي كامل السمك وبقطر ٢ سم في كل الحيوانات وعلى الجهة الوحشية للقائمة الأمامية. في حيوانات المجموعة الأولى والثانية لم تعالج الجروح أما في حيوانات المجموعة الثالثة تم علاج الجروح من خلال التضميد الموضعي بمادة الاندوفورم. تم تقيم نتائج الدراسة من خلال الاعتماد على دراسة التغيرات العيانية والنسجية إضافة الى التحليل الإحصائي بعد ٧، ١٤ و٢١ يوم من إحداث الجرح. أظهرت النتائج العيانية الى التئام الجروح في حيوانات المجموعة الأولى والثالثة بشكل طبيعي. أما الجروح في حيوانات المجموعة الثانية لم يحدث فيها التئام وعانت من التنخر. أما النتائج النسجية المرضية فقد تمثلت في تكوين نسيج حبيبي وارتشاح للخلايا الالتهابية وتكوين أوعية دموية جديدة وعملية تظهر في كل المجاميع. حيث كانت نسبة عملية التظهر في حيوانات المجموعة الثانية بشكل اقل عن حيوانات المجموعة الأولى والثالثة إضافة الى زيادة ارتشاح الخلايا الالتهابية واستمرار تكوين النسيج الحبيبي. بالاستنتاج يمكن استخدام مادة الاندوفورم في تسريع وتحسين التئام لجروح الجلدية في الكلاب المصابة بداء السكري.