



Local application benefits of DL-methionine as wound powder: A novel approach for wound healing process in rabbits

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Abstract

This study examines the clinical and histopathological aspects of using DL-Methionine to enhance wound healing. The purpose of wound management is enhancing healing with minimal pain, discomfort, and scarring; that is important, especially in specific conditions like cosmetic surgery and vital areas injuries like the chest, joints, and eyes where wounds interfere with vital processes, in addition to specific diseases and disorders such as diabetes, mal-immunity, mal-nutrition, and cancer which prolong the healing. Fifteen adult rabbits were used. After surgical preparation, (2cm) diameter circular full-thickness skin wounds were made on each side of the rabbit's back; the control side was left without treatment, while the treated side was covered with 500 mg of DL-Methionine. The experimental wounds were observed daily to assess wound contraction at 6 hours, 1st, 3rd, 5th, 7th, 9th, 12th, and 14th days postoperative. Histopathological analysis was performed on wound edge tissue on the 1st, 3rd, 5th, 7th, and 14th postoperative days. The total healing time for both treated and control wounds was measured. DL-Methionine was effective in hemostasis and accelerated the healing process according to the wound contraction assessment and histopathology due to faster maturation of granulation tissue and epithelial cell proliferation compared to the control group. The fibroblast invasion and increased collagen accumulation in the wound marked the transition from inflammation to proliferation. In conclusion, using DL-Methionine topically on the wound enhances all phases of wound healing, and we can recommend packaging and manufacturing DL-Methionine as a wound powder.

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Introduction

Skin is the largest organ of the body. It has multiple vital functions, such as acting as a barrier between the organism and the environment, which prevents the invasion of extraneous pathogens into the body, sensation, regulating body temperature, and regulating the fluid minerals balance (1,2). A wound disrupts the integrity of the skin, mucosal surfaces, or organ tissue (3). Hence, wound healing has emerged as a prominent area of research within the medical community, particularly in surgical procedures (4). Any

interruptions to the physiological mechanisms of wound healing can give rise to various problems, such as tissue necrosis, microbial infections, and the development of persistent non-healing wounds (5,6). The wound healing process encompasses several vital stages: coagulation, inflammation, granulation tissue formation, matrix formation, connective tissue remodeling, collagenization, and the subsequent gain of wound strength. The process comprises four steps: hemostasis, inflammation, proliferation, and remodeling (7). Understanding the healing process and nutritional influences on the outcomes of wound

healing is critical for the success and management of wounds (8). Several nutritional co-factors that interfere with the tissue repair process have been identified by researchers (9-11) and affirm that wound healing involves a complicated sequence of interactions between different cell types, cytokine mediators, and the extracellular matrix (10,12). Successful wound healing requires an adequate supply of blood and nutrients to the site of the damaged area (12-14). Several factors are known to hinder wound healing – these include but are not limited to infections, hypoxia, tumors, certain medications, protein, vitamins, minerals, a deficient diet, or the presence of debris and necrotic tissue. Inflammation and cellular activity in the healing wound increase the metabolic demand at the wound site, requiring increased protein or amino acids, vitamins, and minerals (15). Historically, many substances have been used to manage the wound-healing process, most notable of which are medicinal herbs, which can be used as primary or secondary therapy. Numerous studies have shown the benefits of topical substances in wound healing (16-22). Amino acids are essential nutritional factors. They are building blocks for DNA, RNA, and proteins. It has been shown that amino acid deficiency affects wound healing (23). Methionine acts as an originator amino acid for important antioxidant molecules such as glutathione, cysteine, and taurine, which play a vital role in detoxification and protect the cells from oxidative damage. Methionine is a 2-amino-4-(methylthio) butanoic acid with one fundamental amino group and neutral. Its zwitterionic form allows the amino group to acquire hydrogen ions from the carboxyl group (24). Methionine has been shown to chelate lead and remove it from tissues; it also has the hydroxyl and peroxy nitrite radicals scavenging ability (25).

The present study aims to evaluate the wound healing process when using DL-Methionine as wound powder by assessing the experimental wounds clinically and histologically and performing wound contraction assessments.

Materials and methods

Ethical approval

Ethical approval was granted through the local committee of animal care and use at the College of Veterinary Medicine within the University of Baghdad (number 2539 on 15/ 11/ 2023) before starting this study.

The materials

DL-Methionine feed grade (Degussa feed additives company) was purchased from local markets for veterinary and agricultural medical supplies.

Animals and surgical preparation

Fifteen healthy local breed rabbits of both sexes were used, with a mean weight of 1.7 kg and ages between 8-12

months. The rabbits were housed indoors in the same condition, fed green grass, and had free access to water. After one week of observation, the animals were prepared for the surgery to make two experimental full-thickness wounds by aseptic surgery (26); general anesthesia was administered by intramuscular injection of xylazine 5mg/kg B.W. followed by midazolam (3mg/kg B.W.) and ketamine (40 mg/kg B.W.) (27). Then, two circular full-thickness wounds, about 2cm in diameter, were made on both sides of the back region using scissors after marking the skin with trephining tools. The right-side wound was treated immediately after wounding with a local application of 0.5g of feed-grade DL-Methionine (Degussa feed additives). Meanwhile, the left-side wound was left for natural healing without any treatment. No surgical suturing was performed, and no additional antiseptic or dressing was used.

Clinical follow-up and wound measurements

The wounds were observed clinically, and wound diameters were measured by digital clipper at 6 hours, the 1st, 3rd, 5th, 7th, 9th, 12th, and 14 days after surgery to record the wound contraction.

Biostatistics

Mean \pm S.D. analyzed data on GraphPad prism software. Tissue samples were obtained for histopathological analyses on the 1st, 3rd, 5th, 7th, and 14th postoperative days. The samples were kept in 10% formalin for 24-48 hours after being collected, and it was ensured that some surrounding healthy areas were included. The formalin-fixed tissue samples were prepared routinely and stained with hematoxylin and eosin for histopathological study.

Results

Histopathologic findings

Clinically, the local application of DL-Methionine on the treated side causes significant hemostasis and prevents blood oozing from the wound compared to the untreated wound. This happened when the powder reacted with the blood, forming a paste-like compound covering the entire wound area, causing the bleeding to stop immediately. Meanwhile, the wound on the control side remained oozing blood for several minutes until normal clotting formed. The wound contraction was observed, and despite that, the results of wound diameter measurement revealed that wounds on both sides (treated and control) appeared greater than the starting point at 0 times, which was supposed to be exactly 2 cm. However, the treated wounds began contracting early after 6 hours of wounding, and the wound diameter dramatically decreased compared to control wounds. The wound contraction was apparent after one day when the mean measured diameter decreased from 2.27 cm to about 1.5 cm. The wound contraction continued daily until it reached complete healing on the 14th of wounding. Clinical

observation also revealed that on the 14th day of wounding, the skin of the treated side returned to normal consistency and elasticity. In addition to that, there was no adhesion between the tiny remnant scar tissue and the underlying

tissue. however, for the control side, the cicatrix of the wound was still considerable, not easily detached, and severely adhered to the subcutaneous tissue. For the wound contraction measurement (Figure 1).

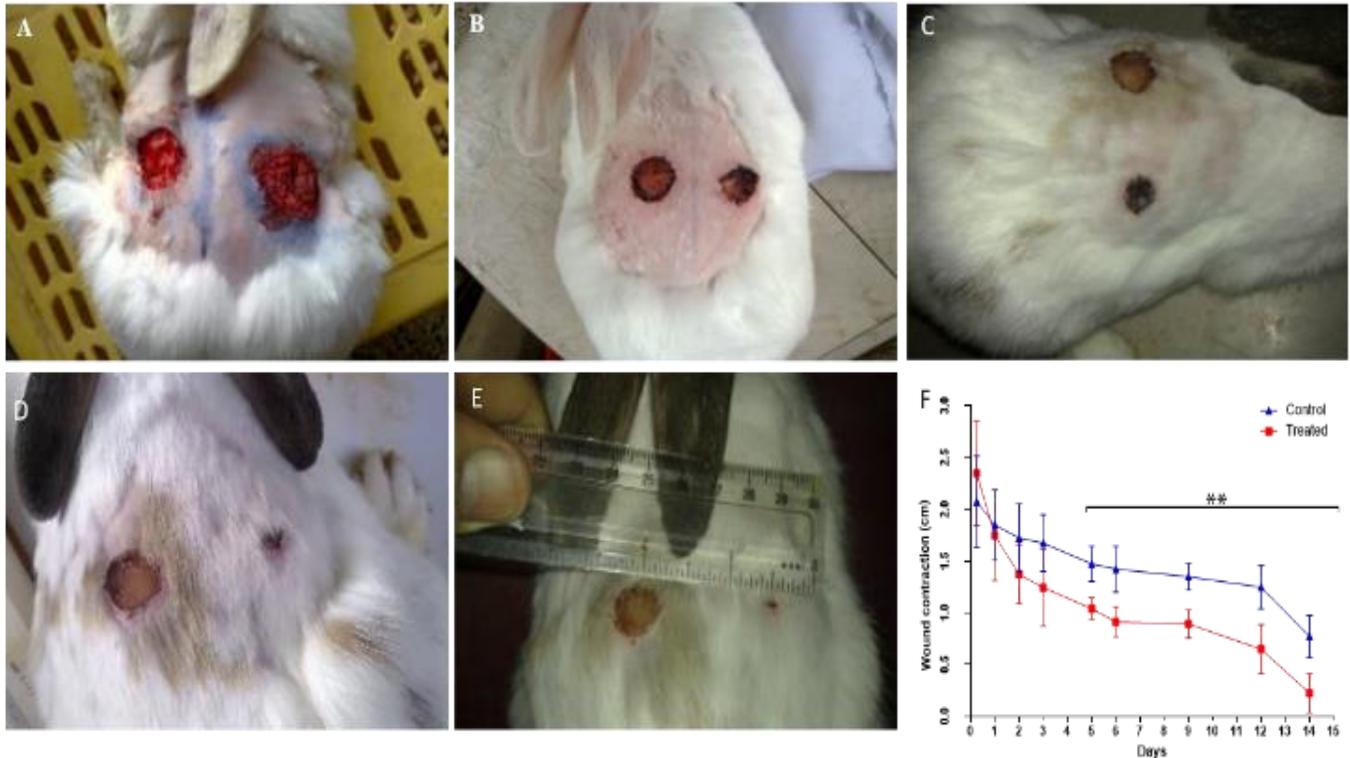


Figure 1: Showed wound contraction after operation; the right side was treated with DL-Methionine powder, and the left side was control (non-treated) at 6 hours (A), first (B), fifth (C), ninth (D), and 14th (E) days after wounding. (F) revealed the wound contraction of each treated and control side (the measurements represent mean \pm S.D. of wound diameter in cm).

Histopathologic findings

The histopathological section of the control wound on the first day shows neutrophil infiltration and edema in the wound section, as well as hemorrhage represented by the area of RBC accumulation. On the treated side, neutrophil infiltration, edema, and a fibrin network are in the wound section. On the third day, on the treated side, the wound edge was settled entirely by immature granulation tissue consisting of primary fibroblasts and newly formed capillaries accompanied by hyperemia and negligible focal hemorrhages. Simultaneously, abundant acute inflammatory cells in the edges and the wound's surface were clear. DL-Methionine in the treated side accelerates the healing process by maturation of granulation tissue and epithelial cell proliferation compared to the control side. The transition from inflammation to proliferation is marked by fibroblast

cells invasion and increased accumulations of the collagen in the wound. Maturation of collagen fiber and formation of total thickness epithelial layer was marked on the 14th day compared with the control side, where there was only a presence of granulation tissue at the wound site with the persistence of few congested blood vessels (Figure 2). The fibroblast invasion and increased collagen accumulation in the wound occurred on the third day on the treated wound side. One of the essential results of this study was an accumulation of granulation tissue and the appearance of epithelial cells in several layers, which means good induction of wound healing, especially on the fifth day. Maturation of collagen fiber and formation of full-thickness epithelial layer was marked at the 14th day comparing with the presence of granulation tissue in the control section's wound site with a few congested blood vassals (Figure 2).

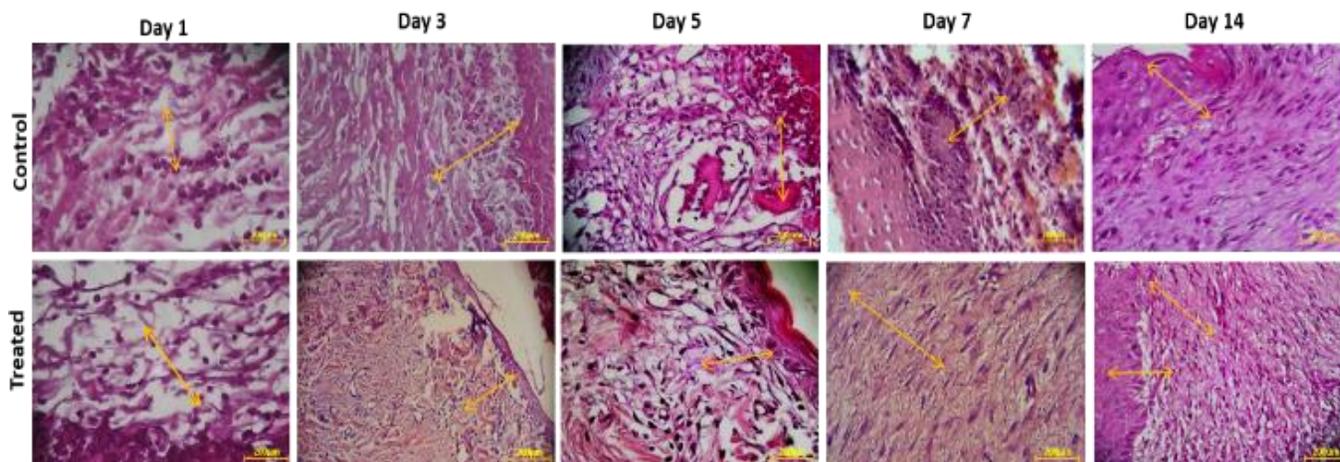


Figure 2: On the first day of control, histopathological examination showed neutrophil infiltration, edema in the incision section, and hemorrhage in the incision; the treated side also showed neutrophil edema and fibrin network in the wound. On the third day, it showed granulation tissues, which consisted of congested blood vessels with irregular connective tissue and inflammatory cell infiltration on the control side. In contrast, the treated side showed mature granulation tissue and epithelial cell proliferation extending from the epidermal layer. On the fifth day of control, the primary lesion is characterized by congestion of blood vessels and inflammatory cell infiltration, particularly macrophages and neutrophils in subcutaneous tissue. However, in the treated section, the epidermis covers the granulation tissue, which consists of several layers of epithelial cells. On the seventh day, mature granulation tissue covered by an epithelial layer consists of a few cells in control. In treated fibrous connective tissue covered by the epithelial layer consists of several layers. On the 14th day, control revealed thickness in the epithelial layer and over-granulation tissue in the incision site with the persistence of a few congested blood vessels. On the contrary, when treated, there is a total thickness of the epidermis layer over the incision area, which is closed by mature collagen fibers. 10X magnification. Scale bar = 200 μ m.

Discussion

For clinical findings, wound healing acceleration can be performed by using topical agents, including ointments, solution, and powder, this acceleration happens by protecting the wound, controlling hemorrhage, and increase of wound epithelialization and contraction (27,28). In this study, all these factors were equipped by using DL-Methionine and confirmed by gross examination and histopathological findings, firstly through immediate hemostasis, and secondly by contraction of both treated and control wound site occurring on the first day of wounding. The treated wound contraction occurs in a faster series and earlier than the control side, this may be due to the presence of methionine which contributes to fibrin synthesis, which in turn is responsible for wound contraction, that normal wound contraction can begin approximately 7 days post-injury and occur at a rate of 0.75 mm/day depending on numerous factors such as the shape and size of the wound (29). In general, linear wounds contract the fastest in comparison to circular wounds, also a week after the fibroblasts start to differentiate into myofibroblasts and begin wound contraction by pulling the edges of the wound together (30).

For histopathological findings, the acceleration of wound healing on the treated side can be explained as amino acids

regulating the activation of immune cells, which produce antibodies and cytokines, such as lymphocytes (B-lymphocytes and T-lymphocytes), macrophages, and natural killer cells, in addition to improving cellular redox status. On the other hand, methionine plays a vital role as an antioxidant, reduces oxidative degradation of the protein, and inhibits chemical degradation (31,32). In addition, the use of oxygen-free radicals is thought to mediate tissue destruction following prolonged venous hypertension caused by venous insufficiency. DL-cysteine, DL-methionine-methyl sulphonium chloride, allopurinol, and dimethyl sulfoxide all bind the oxygen free radicals and so are intended to protect the wounds from further damage released from white blood cells of toxic oxygen metabolites and photolytic enzymes (31,33).

The blood clots and platelets are necessary for hemostasis and provide a temporary matrix for cell migration. Platelets contain α -granules filled with growth factors and cytokines, and vasoactive amines, such as serotonin, that are stored in dense bodies and cause vasodilation and increased vascular permeability, leading to fluid extravasation in the tissue, resulting in edema. Growth factors and cytokines act as promoters by activating and attracting neutrophils and, later, macrophages, endothelial cells, and fibroblasts (34-37). Neutrophils are the first inflammatory cells to appear at the

site of the wound, which can phagocytose bacteria and extracellular matrix. They also release enzymes that break down degenerating connective tissue (37-40).

Consequently, monocytes infiltrate, are attracted by chemotaxis, and are released by aggregating platelets. Monocytes are white blood cells and precursors to macrophages. They are also capable of phagocytosis, and once they have consumed foreign bodies, they transform into macrophages (41,42). The macrophage, not the neutrophil, is essential to wound repair (43,44). In this study, DL-Methionine in the treated side accelerates the healing process by maturation of granulation tissue and epithelial cell proliferation compared to the control side. The transition from inflammation to proliferation is marked by the fibroblast cell invasion and increased accumulation of collagen in the wound (44,45). In avulsion wounds, epidermal cells must extend over the wound surface from the margin of the wound and have a supply of blood and nutrients (46).

The granulation stage starts around four days after wounding and usually lasts until the 21st day in acute wounds, depending on the wound itself. It is indicated clinically by the presence of pebbled red tissue in the wound base and involves the replacement of dermal tissues and sometimes subdermal tissues in deeper wounds, as well as contraction of the wound (47). Meanwhile, DL-methionine accelerated the healing process by maturing granulation tissue and epithelial cell proliferation compared with the control wound. Also, the fibroblast invasion and increased collagen accumulation in the wound occurred on the ^{third} day on the treated wound side. One of the essential results of this study was an accumulation of granulation tissue and the appearance of epithelial cells in several layers, which means good induction of wound healing, especially on the fifth day (48).

The formation of new blood vessels occurs concurrently during all stages of the healing process. The platelets secrete chemical compounds during the hemostatic phase, which attract macrophages and granulocytes and promote angiogenesis. The macrophages play a crucial role in angiogenesis by releasing several other angiogenic substances (41,49). Collagen is a fibrous protein that is synthesized in several stages, and originators are assembled from amino acids in the fibroblast (3).

One of the results of this study was that maturation of collagen fiber and formation of the full-thickness epithelial layer was marked on the 14th day compared with the presence of granulation tissue in the control section's wound site with a few congested blood vessels, this means the presence of DL-methionine enhance the maturation and remodeling process which is supposed to be started when the connective tissue matures and the granulation tissue transitions to scarring. It reduces cellularity as cells are replaced by more collagen (49). Collagen fibrils, which connect several microfibrils, unite, and several of them, in turn, arrange

themselves into bundles. In healthy tissue, the collagen fibers are aligned in a basket weave-like pattern. This organized structure cannot be achieved in wound healing as the collagen fibers at the wound site fashion themselves in an alignment parallel to the stress lines of the wound (50).

Further studies to demonstrate this pathway are needed, and more research is necessary to determine the mode of action of these amino acids to improve wound healing and other tissue healing like bone, nerve, and tendons and stability, as well as stress resistance. In conclusion, the present study on a rabbit wound model indicated that the topical application of DL-Methionine enhances the wound healing process in all phases, and it can be manufactured traditionally as a wound powder.

Conclusion

Using DL-Methionine topically on the wound enhances all phases of wound healing, and we can recommend packaging and manufacturing DL-Methionine as a wound powder.

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Conflict of interest

There was no conflict of interest.

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المناطق الحيوية مثل الصدر والمفاصل والعينين حيث تتداخل الجروح مع العمليات الحيوية، بالإضافة إلى أمراض واضطرابات محددة مثل مرض السكري وسوء المناعة وسوء التغذية والسرطان والتي تطيل فترة الشفاء. تم استخدام خمسة عشر أرنبا بالغاً، بعد التحضير الجراحي، تم عمل جروح جلدية دائرية بقطر (٢ سم) كاملة السماكة على كل جانب من ظهر الأرنب؛ ترك جانب السيطرة دون علاج، في حين تم تغطية الجانب المعالج بـ ٥٠٠ ملجم من الـ ميتاينونين. تمت ملاحظة الجروح التجريبية يومياً، لتقييم تقلص الجرح بعد ٦ ساعات، واليوم ١ و٣ و٥ و٧ و٩ و١٢ و١٤ بعد العملية الجراحية. تم إجراء التحليل النسيجي المرضي على أنسجة حافة الجرح في اليوم ١ و٣ و٥ و٧ و١٤ بعد العملية الجراحية. تم قياس وقت الشفاء الكامل لكل من الجروح المعالجة والمكافحة. كان تطبيق الـ ميتاينونين فعالاً في عملية الإرقاء، وتسريع عملية الشفاء وفقاً لنتائج تقييم تقلص الجرح والتشريح المرضي بسبب النضج الأسرع للأنسجة الحبيبية وتكاثر الخلايا الظهارية مقارنة بالسيطرة. تميز الانتقال من الالتهاب إلى الانتشار بغزو الخلايا الليفية وزيادة تراكم الكولاجين في الجرح. نستنتج بذلك إن استخدام الـ ميتاينونين موضعياً على الجرح يعزز جميع مراحل التئام الجروح، ويمكننا أن نوصي بتعبئة وتصنيع الـ ميتاينونين كمسحوق للجروح.

فوائد الاستعمال الموضعي لمادة د ل ميتاينونين كمسحوق جروح: مدخل حديث لعمليات التئام الجروح في الأرناب

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الخلاصة

تتناول هذه الدراسة الجوانب السريرية والتشريحية المرضية استخدام مركب الـ ميتاينونين لتعزيز التئام الجروح. الغرض من إدارة الجروح هو تعزيز الشفاء، مع الحد الأدنى من الألم والانزعاج والتندب، وهذا مهم، خاصة في حالات معينة مثل الجراحة التجميلية وإصابات