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Silver Sulfadiazine and Boric Acid are Effective in Protecting the Stasis Zone from Secondary Ischemia

Muhammed Salih Süer^{1,*}; Ömer Cennet²; Mehmet Ülkir^{3,✉}; Elham Bahador Zirh^{4,✉}; Ayşegül Fırat³; Ali Konan^{2,✉}

Abstract

A burn wound is characterized by hyperemia on the outer layer, stasis in the middle zone, and coagulation zones in the innermost region due to thermal damage to the skin. It is crucial to provide prompt and adequate treatment to prevent further damage. The depth of the burn increases as ischemic indicators become more distinct in the stasis zone when the burn is not adequately treated, despite the absence of ischemic signs in the stasis zone at the initial stages of the wound.

This study aims to assess the impact of silver sulfadiazine, boric acid, low-molecular-weight heparin, and glyceryl trinitrate on wound healing in the stasis zone. The study involved 4 intervention groups, each consisting of 6 rats, and a sham group. After 7 days of daily topical application of the active substances, the animals were sacrificed, and wound healing in the stasis zones was evaluated through macroscopic, histological, and immunohistochemical analysis. These findings demonstrate the effectiveness of these treatments in promoting wound healing.

The results demonstrated that the boric acid and silver sulfadiazine groups exhibited the highest levels of wound healing, both macroscopically and histologically. Immunohistochemistry revealed significant differences, with the silver sulfadiazine group demonstrating superior results in MMP9 staining and the boric acid group in VEGF staining ($P < .05$). These findings suggest that boric acid and silver sulfadiazine effectively prevent ischemia in the stasis zone. Boric acid, in particular, appears to have significant potential as a wound-healing agent due to its anti-inflammatory properties.

INTRODUCTION

Advancements in burn treatment have led to a reduction in morbidity and mortality. One notable aspect is the stasis zone, which was defined by Jackson and consists of 3 regions: the outermost hyperemic zone, the intermediate stasis zone, and the innermost coagulation zone.^{1,2} Early initiation of fluid resuscitation and early excision and grafting are among these developments that have contributed to this progress.³ Leaving the stasis zone untreated may result in the expansion of the

coagulation zone, which can lead to tissue loss and the development of necrotic tissues, as well as both systemic and local complications. The release of cytokines from necrotic tissues may cause systemic effects, resulting in complications such as systemic inflammatory response syndrome, sepsis, and organ dysfunction.⁴ Infections that may arise in necrotic tissues can result in local complications. As a result, it is important to safeguard the non-necrotic stasis zone from ischemia during the initial stages of a burn.

In the original study observing 1200 burn patients, Jackson explained the changes that occur when a tourniquet is applied. Initially, the color in the hyperemia zone turns white, but upon opening the tourniquet, the color returns, indicating that circulation continues in the hyperemia zone. After 10 minutes of application, the hyperemia zone becomes cyanotic. In the stasis zone, whitening and circulatory signs are observed in the first stage, similar to the hyperemia zone. However, it should be noted that there is no cyanosis in the stasis zone after 10 minutes of tourniquet application, suggesting that metabolism may be impaired in the stasis zone.⁵

The pathophysiology of the stasis zone is of interest. In his original study, Jackson found that in the early stages, circulation in the stasis zone continued but metabolism slowed. However, in the following days, the circulation in the stasis zone became impaired and ischemic signs developed. The reasons leading to this situation are the focus of research.

¹Etlik City Hospital, General Surgery Clinic, Ankara, Turkey ²Department of General Surgery, Hacettepe University, Ankara, Turkey ³Department of Anatomy, Hacettepe University, Ankara, Turkey ⁴Department of Histology and Embryology, TOBB University of Economics and Technology, Ankara, Turkey

*Corresponding author: Muhammed Salih Süer, (suersalib@gmail.com).

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The stasis zone may be adversely affected by inflammatory mediators released from the coagulation zone, where necrosis develops. In addition, impaired capillary circulation and vascular permeability may play a role in this pathophysiology.

The drugs utilized in this study were meticulously selected not only to investigate their effects within the stasis zone but also to enhance our comprehension of the underlying pathophysiology within this area. Silver sulfadiazine was selected for its potent antimicrobial properties, which serve to reduce bacterial contamination and prevent infections in burn wounds. Boric acid is renowned for its anti-inflammatory effects, which facilitate wound healing by increasing cell proliferation, migration, and growth factor expression. LMWH has been demonstrated to be effective in preventing microthrombus formation, improving blood flow, and reducing ischemia at the site of stasis. Glyceryl trinitrate has been shown to increase nitric oxide (NO) levels, which in turn increases vascular permeability and promotes better blood flow to affected areas. By understanding these mechanisms, it is possible to appreciate the rationale behind the choice of these agents to assess their effect on wound healing at the site of stasis.

Boric acid is a topical agent that has been used for many years and has been shown to accelerate wound healing. Boric acid has been shown to increase cell proliferation on the skin, increase cell migration, increase growth factors, and DNA expression. It also reduces DNA double helix breaks.⁶

Burns disrupt the protective barrier against microorganisms, one of the most important functions of the skin. Silver sulfadiazine has a prophylactic effect against infection in the burn wound.⁷ It has side effects such as chemical cellulitis, allergic reactions, silver staining, methemoglobinemia, hemolysis, and leukopenia. It quantitatively reduces bacterial contamination of the wound site.⁸

Microangiopathy, which can result from thrombosis and increased ischemia, is a potential pathology in the stasis zone. A study on comb burns with LMWH (low-molecular-weight heparin) found that heparin may reduce ischemia.⁹ However, it is worth noting that LMWH, which is often studied in cancer research, has been shown to have a negative effect on angiogenesis.¹⁰ Clinical trials have shown that heparin can increase capillary blood flow and decrease healing time in burns and diabetic foot ulcers.¹¹ It is important to note, however, that heparin may not be as effective in populations with malnutrition and vascular problems.

Another way to restore microcirculation may be through the action of nitrates. It works by increasing the level of NO (Nitrous oxide) in the tissues. Glyceryl trinitrate, widely used in general surgery for anal fissure, a benign perianal condition, has been shown to accelerate wound healing after hemorrhoidectomy.¹²

Aim of the study

The purpose of this study is to evaluate the effects of silver sulfadiazine, boric acid, low-molecular-weight heparin, and glyceryl trinitrate on wound healing in the stasis zone of burn injury. The stasis zone, characterized by impaired capillary circulation, increased vascular permeability, and significant inflammation, is highly susceptible to secondary ischemia if not treated promptly. By investigating the underlying mechanisms and pathophysiology, we seek to determine how these agents

can mitigate ischemic damage, reduce inflammation, and promote healing in the stasis zone.

MATERIAL AND METHOD

Animal model

This study was approved by the Hacettepe University Local Ethics Committee for Animal Experiments (Approval date: April 11, 2023, Registration number: 2023/16, Decision number: 52338575-31). The experimental phase was conducted at the Hacettepe University Experimental Animal Practice and Research Center. The study was supported by Hacettepe University Scientific Research Projects Unit (Project ID: 20795).

Thirty male Wistar albino rats were divided into 5 groups, each containing 6 rats. Group 1 treated with Silver Sulfadiazine (Silverdin %1 40 g cream, Deva, Istanbul), Group 2 treated with boric acid (Borik Asit 100 g, Galenik, Istanbul), Group 3 treated with LMWH (Clexane 4000Ü/0.4 mL Sanofi, Istanbul), Group 4 treated with Glyceryl trinitrate (Anrecta %0.4 rectal ointment, Consentis, Istanbul), Group 5 with no treatment as sham.

The animals were anesthetized using intraperitoneal administration of 90 mg/kg ketamine and 10 mg/kg xylazine. In order to induce consistent burns while minimizing harm to the surrounding tissue, burns were created on the dorsal regions after the hair was removed with an electric razor. A brass comb, weighing 130 g, was heated to a temperature ranging from 97 to 103°C by immersing it in boiling water for a period of 10 minutes, and was then applied to the dorsal skin for a duration of 30 seconds (Figure 1). The pressure exerted during application was standardized by allowing the comb to rest on the skin under its own weight, without the application of additional force. The burns were positioned 2 centimeters laterally from the spine and 3 centimeters caudally from the ears, with the objective of ensuring uniform placement across subjects. Postprocedure, subcutaneous administration of paracetamol (10 mg/kg) and buprenorphine (0.05 mg/kg) was conducted for pain management, while paracetamol (30 mg/L) was dissolved in the drinking water to ensure continuous analgesia. Each topical agent was applied and dressed daily according to the designated treatment groups, and the animals were housed individually with ad libitum access to food and water.

Photographic analysis

The specimens were photographed on wooden surfaces alongside a ruler and the images were then transferred to a computer. In AutoCAD® 23 (Autodesk, 2018), the dimensions in the photos were optimized using the rulers. The sizes of all stasis zones were measured using the Polyline technique, and ischemic areas were also calculated using the same technique. The ratios of the ischemia-protected area to the stasis zone were calculated for each segment.

Histological staining

Following sacrifice, the specimens were labeled as A, B, C, D, and E to ensure impartial evaluation of the experimental

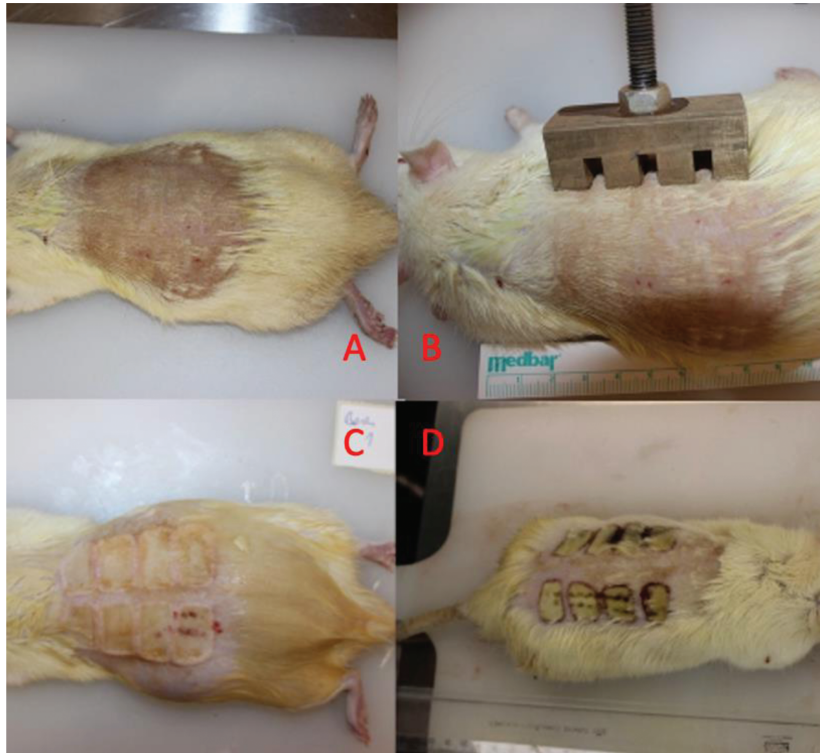


Figure 1. Sequential steps in the creation and progression of the burn wound. (A) The shaved dorsal surface of the rat prior to burn injury preparation. (B) The comb device positioned on the dorsal surface of the rat to create the burn injury. (C) The immediate appearance of the burn wound following injury induction. (D) The appearance of the burn wound on day 7, demonstrating wound progression and tissue changes.

groups during histological assessment. On the 7th day, rats with induced burns were sacrificed for histopathological sampling. All 6 created zones of stasis were sampled from each animal for histopathological evaluation. Each block containing 2 burn zones and the ischemic area in between was dissected and collected for analysis. The collected samples underwent a fixation process in 10% buffered formalin for 24–36 hours. Subsequently, they were processed for tissue tracking and embedded in paraffin. Finally, 4- μ m-thick sections were obtained for Hematoxylin-Eosin (H&E), Masson's trichrome, and immunohistochemical (IHC) staining.

Masson's trichrome staining was performed to assess collagen deposition. Collagen fibers were visualized as blue, nuclei as black, and cytoplasm/muscle as red. The collagen score was quantified semi-quantitatively by 2 blinded observers using a 0–3 scale:

- 0: No collagen deposition.
- 1: Mild deposition (scattered collagen fibers).
- 2: Moderate deposition (organized collagen bundles in <50% of the field).
- 3: Extensive deposition (dense collagen bundles in >50% of the field).

Ischemic areas were scored on a scale of 1–4, similar to clinical burn grading:

- 1: 1st-degree ischemia (limited to the epidermis),
- 2: 2a-degree ischemia (reaching the upper 1/3 of the dermis—superficial—with preserved skin appendages),

- 3: 2b-degree ischemia (reaching the middle 1/3—moderate—with damaged skin appendages),
- 4: 3rd-degree ischemia (reaching the lower 1/3 of the dermis—deep—with damage to the entire dermis).

To evaluate inflammation density, the number of inflammatory cells (neutrophils, lymphocytes, and macrophages) in both the epidermis and dermis was tallied at a magnification of $\times 40$. The sections were stained with H&E, and a 4-tiered system was used to score inflammation density as follows:

- 0: No inflammation.
- 1: Mild inflammation (1–10 inflammatory cells per high-power field).
- 2: Moderate inflammation (11–20 inflammatory cells/HPF).
- 3: Severe inflammation (>20 inflammatory cells/HPF).

IHC staining

For the immunohistochemical examination, sections were treated with antibodies against collagen, vascular endothelial growth factor (VEGF), and matrix metalloproteinase (MMP), which could assess tissue healing and the degree of damage. The MMP9 antibody was used to evaluate extracellular matrix damage, the VEGF antibody for angiogenesis, and the collagen antibody for tissue regeneration.

Antigen retrieval was performed by heating sections in citrate buffer (pH 6.0) at 95°C for 20 minutes, followed by blocking endogenous peroxidase activity with 3% H_2O_2 for

15 minutes and nonspecific binding with 5% bovine serum albumin for 30 minutes. Primary antibody incubation with anti-MMP9 was conducted overnight at 4°C, followed by application of HRP-conjugated secondary antibodies (e.g., anti-rabbit IgG, 1:500) for 1 hour at room temperature, and detection using diaminobenzidine (DAB) (brown signal indicating positive protein staining) with hematoxylin counterstaining (blue nuclei).

The samples subjected to Hematoxylin-Eosin and immunohistochemical staining were covered with Entellan and coverslips, and evaluation was performed at $\times 10$, $\times 40$, and $\times 100$ magnifications using a light microscope (Leica DM 6000B trinocular upright microscope, DC490 digital camera-Leica Microsystems GmbH, Wetzlar, Germany).

Histoscore (H-score) was calculated for MMP9 and VEGF. Five random fields per section were evaluated. The H-score was calculated as

$$H\text{-score} = \sum (\text{intensity} \times \% \text{ positive cells}),$$

Where the intensity was graded as

0 = no staining, 1 = weak, 2 = moderate, 3 = strong.

The final score ranged from 0 to 300 (e.g., 100% weak staining = 100; 50% strong staining = 150).

Statistical analysis

The data obtained from macroscopy, histochemistry, and immunohistochemistry were analyzed using IBM SPSS v23 software. For normal distribution analysis, the Shapiro–Wilk test was applied, and for data showing normal distribution with more than 2 variables, One-way ANOVA test was conducted,

followed by Tukey’s analysis for pairwise comparisons between groups. For data that did not exhibit normal distribution, the Kruskal–Wallis test, a non-parametric test for more than 2 independent variables, was performed. A significance level of $P < .05$ was considered statistically significant.

RESULTS

Macroscopic findings

The specimens obtained by sacrificing the animals at the end of 7 days were photographed for macroscopic evaluation using Autocad software. To obtain a proportional preserved area ratio for each comb burn area, the areas preserved from ischemia were divided by the total surface area. These ratios ranged from 0% to 100%. At the end of 7 days, the ratio of areas that did not progress to ischemia to total areas was calculated for the groups.

The ratio of the area protected from ischemia to the total surface area was 11% in the sham group, 31% in the GTN group, 36% in the silver sulfadiazine group, 57% in the boric acid group, and 18% in the LMWH group. Accordingly, the proportion of areas that did not progress to ischemia was highest in the boric acid group (Figure 2). Due to the non-parametric distribution of these data, Kruskal–Wallis and Tamhane’s tests showed that there was no statistically significant difference ($P = .355$).

Histological findings

Wound healing in the groups was evaluated with Hematoxylin–Eosin and Masson trichrome applied in histologic examination. Ischemia, inflammation intensity, and collagen amounts

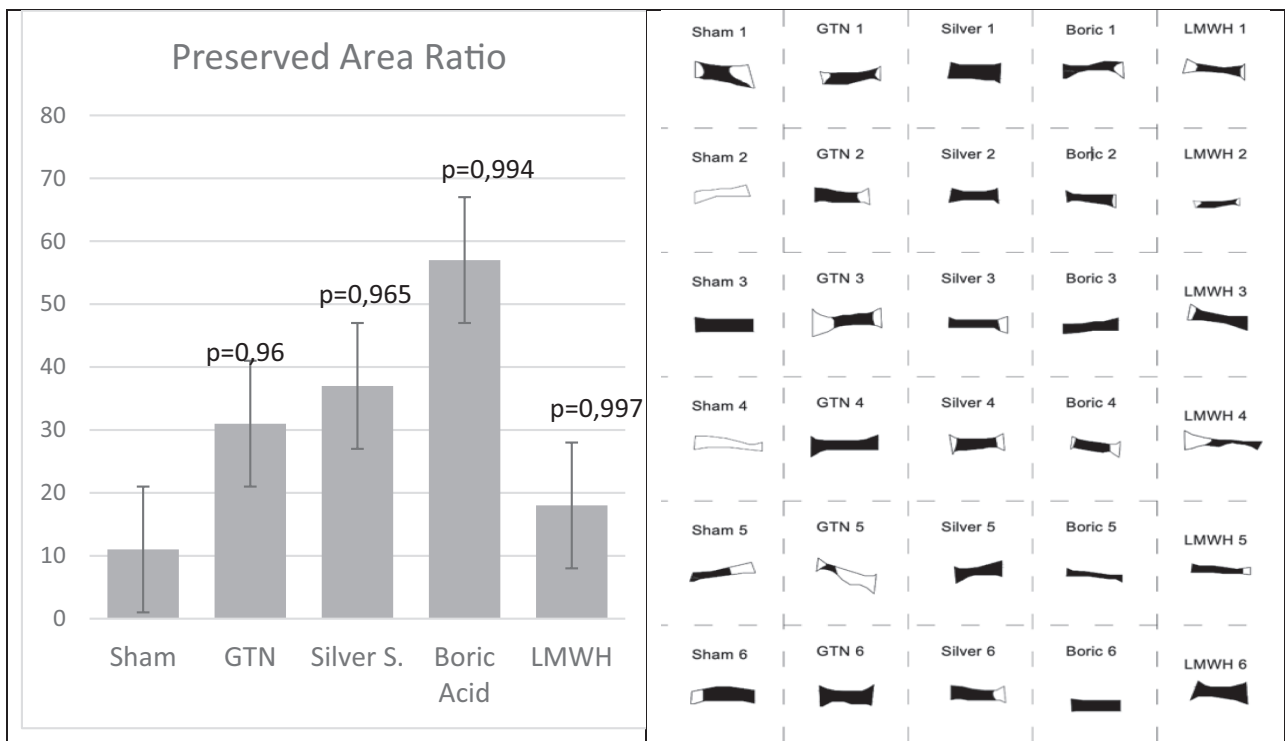


Figure 2. At the end of 7 days, the stasis areas protected from ischemia in the photographs obtained were measured with the polyline technique in Autocad software. Left: A bar graph comparing the preserved areas in different treatment groups at the end of 7 days. The preserved areas are quantified and displayed as a percentage of the total burn area. Right: Polyline drawings obtained using AutoCAD software, showing the burn wound areas. The white regions represent the burned (ischemic) areas, while the black regions represent the preserved areas that were protected from ischemia.

Table 1. Ischemia, inflammation, and collagen density scores obtained by hematoxylin-eosin staining and Masson trichome staining. The highest score for collagen amount is in the boric acid group, the highest score in inflammation intensity is in the sham group, the highest score in ischemic area was found in the GTN group

Groups	Collagen score	Inflammation score	Ischemia score
Sham	0.70	2.40	3.50
GTN	0.57	2.00	3.67
Silver sulfadiazine	2.07	0.63	1.50
Boric acid	2.47	0.53	1.00
LMWH	1.47	1.40	2.67

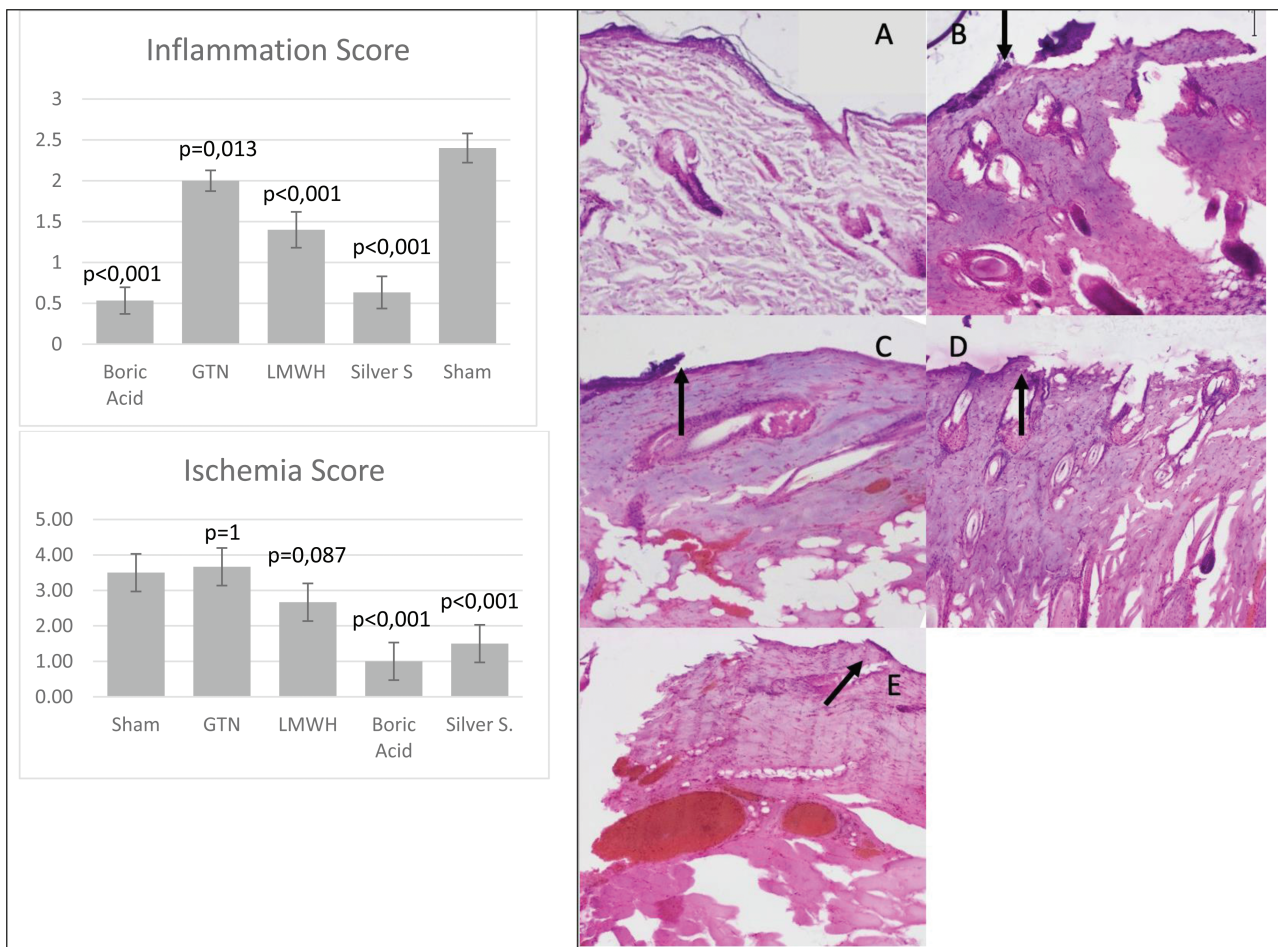


Figure 3. Micrographs ($\times 100$) of Hematoxylin–Eosin stained preparations of the groups are presented. Scar areas are indicated by an asterisk and the border of the area that is not yet epithelialized is indicated by a thin arrow. Inflammation intensity and ischemic area scores were obtained through Hematoxylin–Eosin staining. A graph of inflammation intensity scores in Hematoxylin–Eosin staining is provided for each group. The histologic findings of wound healing are also presented, along with a graph of ischemic area scores according to groups. Images are oriented with the epidermis at the top and the deep region at the bottom. (A) Boric acid, (B) glyceryl trinitrate, (C) LMWH, (D) silver sulfadiazine, (E) sham.

were scored in the micrograph ($\times 100$) sections and the mean values of the groups were given in Table 1. Each magnification area was scored in terms of ischemia area, inflammation intensity, and collagen amount as described in the materials and methods section.

In Figure 3, the results of the histological evaluations are summarized, and as can be seen, the inflammation score was

highest in the sham group, the ischemia score was highest in the GTN group, and the collagen density was highest in the boric acid group.

As demonstrated in Figure 3, the boric acid and silver sulfadiazine groups exhibited the greatest capacity to safeguard the stasis zone from ischemia. In conjunction with this figure, Figure 4 illustrates the quantification of collagen densities

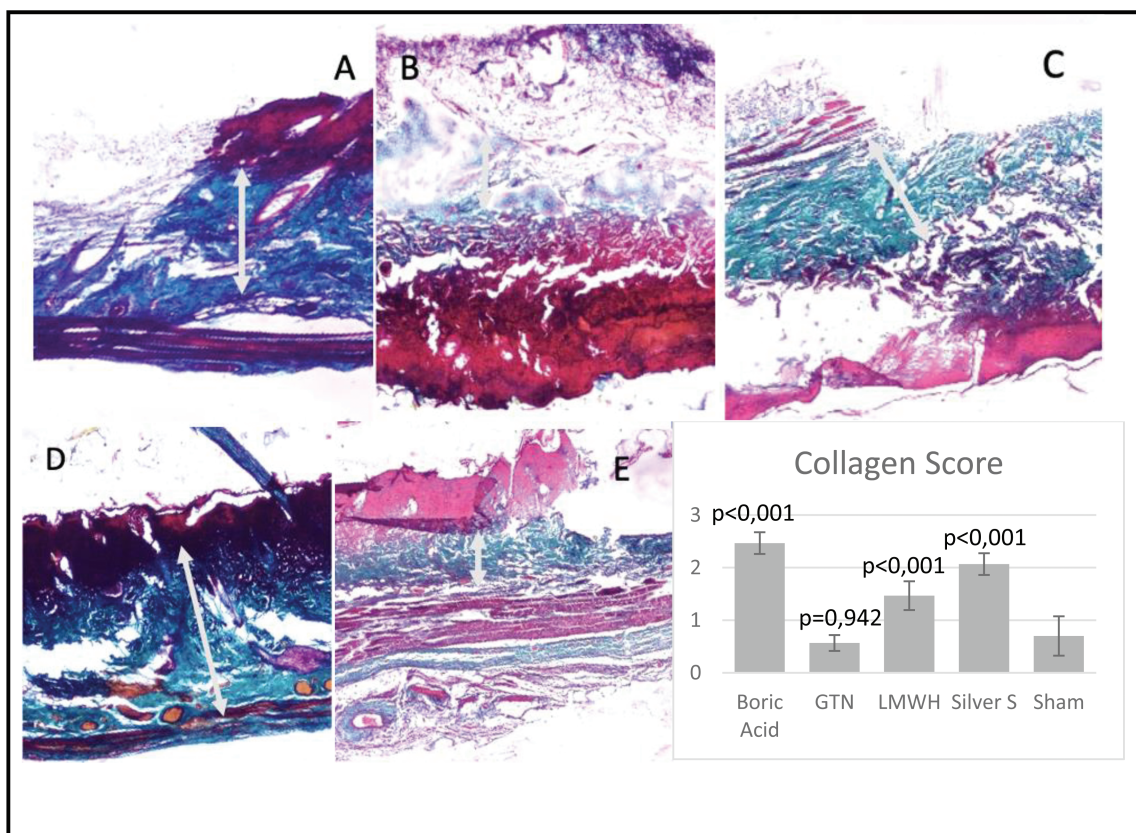


Figure 4. Micrographs ($\times 40$) of Masson trichrome stained preparations of the groups are presented. The bidirectional arrow indicates dermis thickness, which is reduced in the sham and GTN groups. Collagen density scores were calculated using Masson trichrome staining. A graph displays the distribution of the scores calculated according to collagen density in Masson trichrome staining for each group. Images are oriented with the epidermis at the top and the deep region at the bottom. (A) Boric acid, (B) glyceryl trinitrate, (C) LMWH, (D) silver sulfadiazine, (E) sham)

through Masson trichrome staining. In both figures, the boric acid and silver sulfadiazine groups demonstrated a statistically significant superiority.

Immunohistochemical results

Immunohistochemical analysis of VEGF and MMP9 staining revealed that the Boric Acid and Silver Sulfadiazine groups demonstrated significantly higher histoscores compared to the other treatment groups ($P < .01$). These results indicate enhanced expression of VEGF and MMP9 in these groups, suggesting better outcomes in terms of tissue response (Figure 5). In contrast, the Sham group exhibited the lowest histoscores for both markers, highlighting its comparatively poor performance.

DISCUSSION

The results of this study highlight the efficacy of silver sulfadiazine and boric acid in protecting the stasis zone from secondary ischemia, both of which have been shown to improve burn wound healing.¹³ Although these wounds did not become infected, even in the absence of SSD (silver sulfadiazine) treatment, the protective mechanisms of SSD extend beyond infection prevention. SSD has been shown to modulate the

inflammatory response and mitigate tissue damage in the stasis zone.^{14,15} Boric acid, on the other hand, showed significant results in promoting wound healing, supported by its known anti-inflammatory properties and ability to enhance cell proliferation and growth factor expression.^{16,17}

Silver sulfadiazine anti-inflammatory effect

The experimental animals that received treatment with silver sulfadiazine exhibited a reduction in ischemia and inflammation in the stasis zone. Furthermore, there was a significant increase in the amount of collagen, VEGF, and MMP9 scores. Although there were no significant macroscopic changes, the microscopic findings suggest that silver sulfadiazine may have protective effects.

Silver sulfadiazine is a reasonable topical agent due to its protective effects against infection and secondary damage in the stasis zone, despite reports in the literature suggesting it may impair epithelialization.^{15,18-20}

Boric acid protects the stasis zone

Boric acid is an effective local treatment for wounds, accelerating wound healing and protecting the stasis zone in burn wounds through its anti-inflammatory activity. Despite

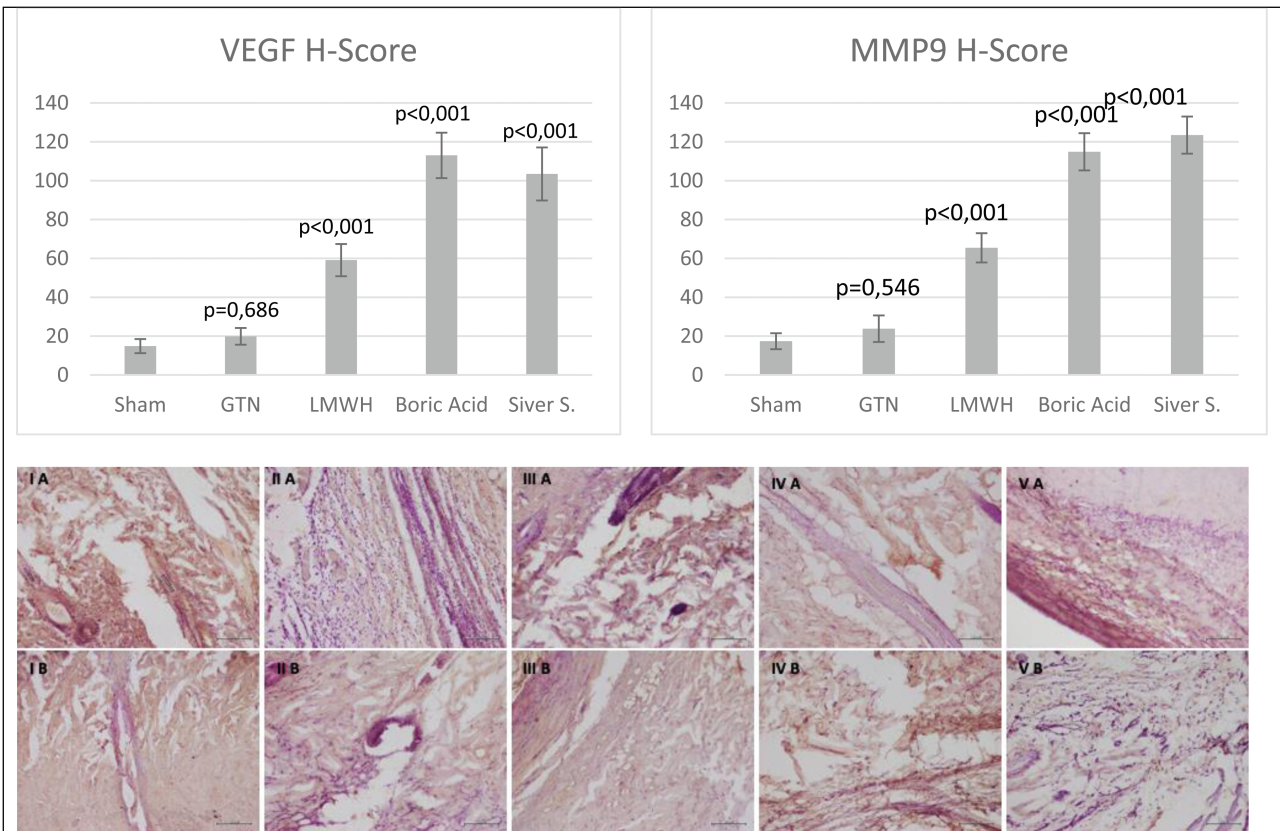


Figure 5. The distribution graph displays the VEGF histoscores for each group, while the MMP9 H-score distribution is shown separately. The top row of micrographs ($\times 200$) shows the indirect immunoperoxidase staining images of VEGF antibody, and the bottom row shows the micrographs ($\times 200$) obtained after the application of indirect immunoperoxidase labeling of MMP9 antibodies to the sections of the groups. (I: boric acid, II: glyceryl trinitrate, III: LMWH, IV: silver sulfadiazine, V: sham)

its potential benefits, boric acid is currently underutilized in burn wound treatment and deserves further attention. Furthermore, the immunohistochemical data indicated that silver sulfadiazine exhibited superior MMP9 staining, suggesting its significant role in controlling extracellular matrix degradation. In contrast, boric acid demonstrated significantly higher VEGF expression, indicating its potential in promoting angiogenesis and tissue regeneration. These findings support the hypothesis that boric acid may play a more substantial role in enhancing vascular repair compared to silver sulfadiazine, which predominantly prevents infection and controls inflammatory responses.²¹

Heparin and ischemia

LMWH disrupts angiogenesis and inhibits microthrombi. Although systemic use of LMWH can have side effects on the hematopoietic and gastrointestinal systems, previous studies have shown its effectiveness in the stasis zone when applied systemically compared to the sham group.^{22–25} Unlike prior studies where LMWH was administered subcutaneously, this study employed topical application to avoid systemic side effects while targeting the stasis zone directly. In our study, topical application of LMWH produced better outcomes than the sham group, supporting its efficacy in the stasis zone without systemic side effects. The boric acid and silver

sulfadiazine groups showed the most favorable outcomes, suggesting that the anti-inflammatory effect has a significant impact on the stasis zone.

Glyceryl trinitrate is ineffective

Although NO is widely recognized in the literature for its ability to accelerate wound healing by promoting vascular permeability, its effectiveness in protecting the stasis zone when topically applied as glyceryl trinitrate (GTN) has not been well-established.²⁶ One potential explanation for this discrepancy may lie in the bioavailability of the ointment at the burn surface. The burn-induced changes to skin structure, such as increased barrier permeability or reduced absorption efficiency, may hinder the effective delivery of GTN to the underlying tissues. Additionally, the concentration and formulation of the topical agent may play a crucial role in its efficacy at the site of injury.

CONCLUSION

In conclusion, the results of this study demonstrate that silver sulfadiazine and boric acid are effective in protecting the stasis zone from secondary ischemia in a rat model of burn injury. Both agents demonstrated notable improvements in wound

healing, both macroscopically and histologically. Of the 2, silver sulfadiazine exhibited particularly pronounced efficacy in reducing extracellular matrix degradation, while boric acid demonstrated a marked capacity to enhance angiogenesis and tissue regeneration. These findings suggest that boric acid, with its anti-inflammatory properties and promotion of tissue repair, may serve as a valuable addition to burn wound treatment protocols, in conjunction with the well-established use of silver sulfadiazine for infection control. Further studies should investigate the long-term effects and potential synergies between these agents to enhance burn care management. Additionally, the current data indicate that the limited effectiveness of glyceryl trinitrate and LMWH in preventing ischemia warrants further investigation into their role in the complex pathophysiology of burn injuries.

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