

# Treatment of open wounds secondary to trauma using polyurethane foams with boric acid particles

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## ABSTRACT

**BACKGROUND:** To investigate the efficacy of new foams with boric acid particles combined with a negative pressure wound treatment (NPWT) system in open fractures with tissue defects secondary to trauma.

**METHODS:** Forty-nine patients with open fractures secondary to trauma with soft tissue defects who were admitted between 2016 and 2018 were included in the study. Patients were examined in two groups. In Group 1, boric acid-impregnated foams combined with the NPWT system were used in 27 patients, and in Group 2, silver nitrate-impregnated foams combined with NPWT systems were used in 22 patients. In addition to evaluating the broad-spectrum antibacterial feature of silver nitrate, the antimicrobial, angiogenic, and epithelializing effects of boric acid were investigated macroscopically and histopathologically.

**RESULTS:** A reduction in wound size and granulation was observed in each group. Macroscopically, the reduction in wound size, epithelialization and granulation were pronounced in Group 1 and in Group 2. Microscopically, the number of fibroblasts, collagen synthesis, and angiogenesis were significantly increased in Group 1 compared with Group 2.

**CONCLUSION:** In this clinical trial, both the broad spectrum antimicrobial feature of boric acid and its positive effect on the cells responsible for wound healing were found to be an alternative compared with silver nitrate. The use of new foams with boric acid particles combined with the NPWT system may be a good alternative method in the treatment of open wounds due to trauma.

**Keywords:** Boric acid particle; boron foams; the negative pressure wound therapy.

## INTRODUCTION

Today, cellular mechanotransductivity, that is, the relationship between mechanical forces and wound healing is well understood. This characteristic led to the introduction of the negative pressure wound treatment (NPWT) system, which has taken its place among today's modern wound treatment methods. The system comprises negative pressure, wound contact intermediate material, and substances contained in this intermediate material. This system is widely used in the treatment of tissue defects in open fractures and chronic, contaminated wounds.<sup>[1-3]</sup> Discussions on the optimal physi-

cochemical structure of the wound contact intermediate material within this system are ongoing.

Today, silver nitrate-impregnated polyurethane foams are used as wound surface intermediate material. Silver nitrate has a broad spectrum antibacterial property, which is a very important advantage. However, the fact that it has significant adverse effects worries physicians (leukopenia, dysfunction of the kidney and liver);<sup>[4-6]</sup> some of the non-dose-related complications of silver nitrate have become seriously questioned. Furthermore, its positive effect on cell proliferation is not yet known.

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Boric acid is a hydrophobic element that is considered to be non-toxic, and to be especially useful for various systems if it does not reach systemically high levels.<sup>[7-9]</sup> Intermediate materials optimally require two features: Broad spectrum antibacterial effect and proliferative activity. Foams with boric acid particles were combined with NPWT to treat acute wounds secondary to trauma because acid boric contains both features. The aim of this study was to conduct macroscopic and histopathologic investigations of the antimicrobial, angiogenetic, and macrophage-stimulating and epithelializing effects of these foams.

## MATERIALS AND METHODS

Forty-nine patients who were admitted to our hospital's emergency department with acute traumatic open fracture and soft tissue injury were included in the study. Five patients whose treatment could not be concluded were excluded from the study. According to the Gustilo Anderson classification, 12 patients with open fractures were type 3A, 22 patients were type 3B, and six patients were type 3C, 9 patients were type 2. This study was planned as a retrospective cohort study. This study was approved by the Local Ethics Committee (Decision No: 277, Date: 12.09.2018). The patients were independently examined in two groups; Group 1 (n=27) was treated using boric acid-impregnated foams combined with NPWT system, and Group 2 (n=22) was treated

with conventional silver nitrate- impregnated foams combined with NPWT system. The general demographics, habits, and comorbidities of the patients were recorded. Three-dimensional wound measurements were performed in the first admission (Tables 1 and 2). Wound debridement and wound size measurements were made in each period (every 5 days) and changes were recorded. Debridements were made in the operating room. Investigations such as biochemical tests, measurement of boric acid levels in urine and serum, total blood count, complete urine analysis, measurement of C-reactive protein levels, and wound cultures were performed at the end of each session during follow-up.

Physicochemical features of foams with boric acid: These foams, created for use as wound surface material, are made of polyurethane ether with 400–600 µm pores and have a wide intake surface. The 2–3% boric acid-impregnated foams are 300×70 micron in size. Boric acid is evenly distributed across the entire polyurethane foam surface.

In Group 2, conventional silver nitrate-impregnated foams (Binosil Turkey, Ankara) were used (2.5–5 µg/mL release). The same brand of the negative pressure generating devices for all patients was used at the same pressure (80–120 mm Hg) and for the same duration.

## Study Outcomes

In addition to the macroscopic evaluation, histopathological evaluation of the specimen prepared from the periphery of the wound was performed. At 5-day intervals, the wound surface materials (foams) were changed with wound debridement, culture and biopsy samples were taken, and the same examinations were made and histologic changes were noted. All patients underwent antibiotic prophylaxis (cefazolin sodium 3×1 g, gentamicin sulfate 2×80 mg) for the first 2 days. In the following days, the patients with isolated a bacteria in wound culture (six patients in two groups) were treated

**Table 1.** Age and wound size means in the groups

	Silver nitrate	Boric acid	p
	Mean±SD	Mean±SD	
Age	33.96±11.45	37.22±9.14	0.272
Wound size	85.91±26.53	79.26±26.04	0.382

SD: Standard deviation.

**Table 2.** Sex distribution, number of sessions, and smoking status of the silver nitrate and boric acid groups

	Silver nitrate		Boric acid		Total		p
	n	%	n	%	n	%	
Sex							
Female	5	22.7	6	22.2	11	22.4	0.999
Male	17	77.3	21	77.8	38	77.6	
Smoking							
Yes	8	36.4	11	40.7	19	38.8	0.754
No	14	63.6	16	59.3	30	61.2	
Number of sessions							
3	10	45.5	11	40.7	21	42.9	0.659
4	9	40.9	14	51.9	23	46.9	
5	3	13.6	2	7.4	5	10.2	

**Table 3.** Semiquantitative evaluation of histological parameters for the assessment of wound healing

Score	Re-epithelialization	Granulation	Inflammatory cells	Angiogenesis
0	0	0	++++	0
+	+	+	+++	+
++	++	++	++	++
+++	+++	+++	+	+++
++++	++++	++++	0	++++

0: Absence; +: Slight; ++: Moderate; +++: Marked; ++++: Ekstensive.

according to the culture antibiogram results. The histopathologic evaluation criteria of the patients were made according to Table 3.<sup>[10]</sup>

### Statistical Analysis

The normality of distribution of continuous variables was checked using the Shapiro-Wilk test. Student's t-test was used to compare age and wound size between the silver and boric acid groups because they showed normal distribution. The distribution of sex, number of sessions, and culture status according to groups was examined using the Chi-square test. The marginal homogeneity test and for 2×2 tables the McNemar test were used in the investigation of changes in re-epithelialization, granulation, inflammatory cells, and angiogenesis rates according to the first, second, and last measurements. The significance level was 0.05 in all analyses.

## RESULTS

Forty-nine patients with soft tissue defects secondary to acute trauma were enrolled in the study. In both groups, the majority of the defective wounds were localized to the lower extremity and to the anterior cruris and dorsal surface of the foot. There was no difference between the age averages and wound sizes of the patients in either group (Table 1). There were 21 men and six women in Group 1, and five women and 17 men in Group 2 (Table 2). Definitive treatments of the patients were performed after VAC treatment and wound closure were completed. In 37 patients (75%), union was achieved after the first surgical intervention, and nine patients required secondary surgical intervention. Amputation was applied to three patients.

Late infection was observed in four patients (two boric acid and two silver nitrate) after definitive treatments and discharge.

The blood and urine levels of boric acid were not measurable in all patients.

There was no statistical difference between either group in terms of smoking and peripheral vascular disease, and inci-

dence rates of diabetes ( $p=0.754$ ). Likewise, there was no difference in age, sex, and bacterial reproduction rates in wound culture between the groups ( $p>0.05$ ). There were no significant differences between the groups in terms of resistant strains and microbiologic assessment. No pathogen was detected in the culture at the end of the 10<sup>th</sup> day in any patient. Duration of hospital stay was 17.3 days in the Group 1 and 19.7 days in Group 2.

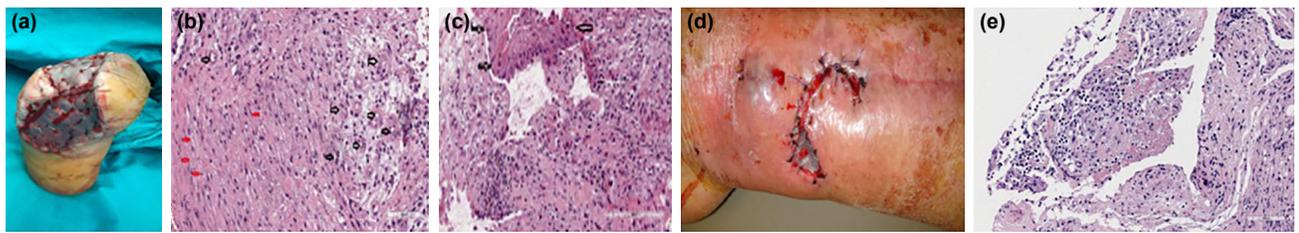
The microscopic quantitative evaluation criteria were made according to Table 3. In this assessment, epithelialization, granulation, inflammatory cell count, and vascular proliferation were taken into account at each session. The foci of necrosis, erythrocytes, damaged arterioles, and inflammation and neutrophils in the first and second sessions were replaced by lymphocytes, fibrosis, granulation, and angiogenesis (Figs. 1 and 2). Although there was vascular proliferation in both groups, vascular proliferation was more pronounced in patients in Group 1 (Fig. 3).



**Figure 1.** In a patient who was admitted with an open fracture of the tibia in whom silver nitrate-impregnated foams were used, PNLs (Red Arrow) and lymphocytes (Black Arrow) were present rather than granulation and fibrosis after the session 2 (H&E 20×). PNLs: polymorphonuclear lymphocytes.



**Figure 2.** In a patient who underwent traumatic amputation and was treated with foams with boric acid, inflammation was replaced by lymphocytes (Black Arrow), fibrosis, and granulation after the session 2 (H&E = hematoxylin and eosin staining ×20).



**Figure 3.** (a-e) Status of grafted wound in two patients after the 4<sup>th</sup> (last) session: Angiogenesis (b black arrow), fibrosis, and epithelialization (c black arrow) were present in Group 1, which was treated with boric acid foams (a-c), and vascular structure and fibrosis were present but epithelialization was not observed in the silver group (lower) (x20) (e).

In Group 1, macroscopic shrinkage in wound size, and epithelialization and granulation were more pronounced than in Group 2. Microscopically, there was a significant increase in fibroblast number, collagen synthesis, and granulation tissue (Fig. 3).

In both groups, re-epithelialization, granulation, and angiogenesis increased positively after each session, there was a decrease in inflammatory cells at the end of each session, and conversion from PNLs (leukocytes) to lymphocytes was observed.

Although there was no statistically significant difference between the two groups in terms of the measurements of four histopathologic parameters after the sessions I, a statistically significant difference was found between the groups in favor of Group 1 in terms of all measurements of the four parameters after the second session and in the last session (Table 4).

In the group that was treated with boric acid foams, about 92% (25/27) success was achieved after repair with a skin

**Table 4.** Histopathological evaluation according to stages

Measure	Re-epithelialization												p	p									
	Silver nitrate						Boric acid																
	0	1	2	3			0	1	2	3													
n	%	n	%	n	%	n	%	n	%	n	%	n	%										
Last	3	13.6	14	63.6	5	22.7	0	0.0	<0.001	0	0.0	6	22.2	15	55.6	6	22.2	<0.001	<0.001				
Measure	Granulation												p	p									
	Silver nitrate						Boric acid																
	0	1	2	3	4		0	1	2	3	4												
n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%						
Last	0	00.0	14	4.5	10	45.5	10	45.5	1	4.5	<0.001	0	0.0	0	0.0	1	3.7	16	59.3	10	37.0	<0.001	<0.001
Measure	Angiogenesis												p	p									
	Silver nitrate						Boric acid																
	0	1	2	3	4		0	1	2	3	4												
n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%						
Last	0	0.0	0	0.0	18	81.8	4	18.2	0	0.0	<0.001	0	0.0	0	0.0	1	3.7	12	44.4	14	51.9	<0.001	<0.001
Measure	Inflammatory cells												p	p									
	Silver nitrate						Boric acid																
	0	1	2	3	4		0	1	2	3	4												
n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%						
Last	0	0.0	2	9.1	15	68.2	5	22.7	0	0.0	<0.001	0	0.0	0	0.0	9	33.3	16	59.3	2	7.4	<0.001	0.001

graft, only one patient needed re-debridement and grafting, and one required a rotation flap. About 77% (17/22) success was achieved in the group treated with silver nitrate foams, three patients underwent re-grafting, one patient had a rotation flap, and one patient had a free flap.

## DISCUSSION

Cellular mechanosensitivity allows many tissues and organs to benefit from the healing potential of mechanical stresses. Mechanical energy applied to cells causes proliferation and migration in cells. The negative pressure applied to the cell alone causes positive effects on the cell. However, many issues in this system remain unclear.<sup>[11,12]</sup> The optimal physicochemical properties of these foams, which are used as intermediate materials, are not yet fully known.

There is evidence that the mechanism of action of the NPWT system is increasingly understood, and it has some beneficial effects. The mechanisms of action of NPWT; create macrodeformation and microdeformation of the wound surface, enable extraction of edematous fluid, provide a warm and moist environment that prevents the desiccation of the wound, and increase the formation of granulation tissue.<sup>[2]</sup> In one study, it was reported that prolonged NPWT duration was associated with bacterial growth, and efforts should be made to reduce the duration of NPWT.<sup>[13]</sup> It was reported that open fractures and increased age prolonged hospital stay, and smoking, alcohol, and drug addiction increased the rate of return to hospital in these patients. No significant increase was reported in those with diabetes mellitus and peripheral vascular disease.<sup>[13]</sup> In this study, we aimed to compensate long hospital stays and increased risk of infection in patients with the antimicrobial properties of silver and boric acid in addition to systemic antibiotic treatment. Patients were discharged after the infection was treated.

According to the results of a systematic review and meta-analysis involving eight randomized controlled trials and six retrospective cohort studies, NPWT was associated with significantly lower infection rates, shorter wound coverage time, wound healing time, length of hospital stay, and lower amputation rates. It was also reported that there was no statistically significant difference in terms of the need for flap surgery, free flap rates, flap failure rates, and rates of failure in repair of fracture.<sup>[14]</sup> In our study, we achieved successful results with the use of split thickness grafts after adequate granulation was achieved with the NPWT system in open fractures with tissue injury that might require free or rotational flaps.

Today, silver nitrate is used as filling material in foams. This combination gives local antimicrobial properties to the foams. Silver is a bactericide of interest due to its effectiveness in both Gram-positive and Gram-negative bacteria. However, at high concentrations, it is toxic to mammalian cells. In addition,

the control mechanism for silver release has not yet been clearly identified. In addition, there is no opinion on what effects will occur in late periods. Finally, very important complications such as leukopenia, dysfunction of the kidney and liver; neuropathy and Argyria are still serious problems of silver.<sup>[15-19]</sup> For these reasons, there is abstention among physicians in the use of silver in medical practice.

Boron-based compounds, on the other hand, have been used for medical purposes for a long time. Boric acid shows significant antimicrobial effects against bacteria, yeast, and fungi, and it significantly increases cellular proliferation, macrophage migration, and also the levels of proteoglycans and growth factor gene expression in dermal cells. It has been reported that it plays an important role in the wound healing process by increasing extracellular matrix (ESM) synthesis through the production of protein and collagen.<sup>[7,9,20-23]</sup> In particular, it shows anti-bacterial, anti-candida, and antifungal activities. Its antibacterial effect on bacteria such as *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Candida albicans*, *Aspergillus niger*, *Escherichia coli*, and *Pseudomonas aeruginosa* has been shown in several studies.<sup>[7,23,24]</sup> In addition, boric acid has been used as a medical product in eye and ear drops, and in the treatment of gynecologic diseases and wounds. We wanted to see the effect of boric acid-impregnated polyurethane foams on acute wounds because it is one of the most important components of the NPWT system due to its broad-spectrum antimicrobial properties, as well as its positive effect on cells responsible for wound healing.

Boric acid is a broad-spectrum agent. However, a single study claimed that acid boric had no antimicrobial effects.<sup>[25]</sup> The authors reported that the antimicrobial effect of derivatives such as acetic acid and ascorbic acid was extreme, whereas boric acid had no antimicrobial properties. However, no other study supporting this claim has been identified by us. The antimicrobial effect of this product was not studied in our study. In acute injuries secondary to trauma, and especially in open fractures, infection is a major problem. In the present study, no microorganisms were detected in cultures in the last period in either group. However, the active agents used in both groups were known to have broad-spectrum antibacterial properties.

Vascular endothelial growth factor and fibroblastic growth factor are the two factors responsible for new tissue formation. On the other hand, it is a well-known fact that cellular stress forces are necessary for cells to hold on to growth factors and ESM proteins. In wound healing, these two factors, namely, growth factors and cellular retention, are two very important parameters.<sup>[26-30]</sup> Boric acid has been shown in several studies to significantly increase cellular proliferation, macrophage migration, level of growth factor, and gene expression level in dermal cells.<sup>[30]</sup> In our study, we obtained high levels of vascular proliferation and granulation tissue in patients treated with boric acid.

The formation of capillary vessels is primarily responsible for wound healing. Some authors claimed that boric acid had no significant effect on angiogenesis, or even prevented it.<sup>[30]</sup> It is difficult to make clear statements about the effect of boric acid on angiogenesis with our study because it is a known fact that this negative-pressure device has angiogenic properties. In our study, findings of angiogenesis were observed from the 10th day in the group treated with boric acid. The statistically significant difference between the two groups in our study may suggest that boric acid plays an important role in angiogenesis.

There were some limitations to study. The patients were randomly divided into groups. The number of patients participating in the study was limited. The current work that needs to be validated with a much larger randomized PCT. A comprehensive prospective study has been initiated by us.

## Conclusion

Positive results in terms of infection and wound healing were achieved in both groups. It was observed that wound healing times were shortened by the application of foams with boric acid. We believe that boric acid-impregnated foams, besides their antimicrobial properties, have a much better synergistic effect with the negative pressure generating system on cell proliferation, differentiation, and migration, which are necessary for wound healing. In addition, the increase in vascular proliferation (angiogenesis) and fibroblast number and function beginning from the second session was remarkable. In all wounds, all phases were shortened and cell proliferation, migration, and differentiation occurred much faster.

**Ethics Committee Approval:** This study was approved by the Adana City Training and Research Hospital Local Ethics Committee (Date: 12.09.2018, Decision No: 277).

**Peer-review:** Internally peer-reviewed.

**Authorship Contributions:** Concept: H.U.O.; Design: H.U.O.; Supervision: H.U.O.; Resource: H.U.O.; Materials: H.U.O., R.K., Ö.K., V.T.T.; Data: H.U.O., R.K., Ö.K., V.T.T.; Analysis: O.Ç., A.Y.; Literature search: O.Ç., A.Y.; Writing: H.U.O.; Critical revision: O.Ç.

**Conflict of Interest:** None declared.

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## ORJİNAL ÇALIŞMA - ÖZ

### Travmaya sekonder açık yaraların borik asit parçacıklı poliüretan süngerle tedavisi

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**AMAÇ:** Travmaya sekonder doku defekti mevcut açık kırklarda, Negatif Basıncılı Yara Tedavi (NPWT) sistemi ile kombine borik asit parçacıklı süngerin etkinliği araştırılmak istendi.

**GEREÇ VE YÖNTEM:** 2016–2018 yılları arası travmaya sekonder açık kırığı mevcut, yumuşak doku defektinde olan 49 hasta çalışmaya dahil edildi. Hastalar iki grupta incelendi. Birinci gruptaki 27 hastaya NPWT sistemi ile kombine, yeni bir yöntem olan borik asit emdirilmiş sünger, ikinci gruptaki 22 hastaya NPWT sistemi ile kombine gümüş nitratlı sünger kullanıldı. Gümüş nitratın geniş spektrumlu antibakteriyel özelliğinin değerlendirilmesinin yanında, borik asitin antimikrobiyal, angiogenetik ve epitelizan etkileri, makroskopik ve histopatolojik olarak araştırıldı.

**BULGULAR:** Her iki grupta yara boyutunda küçülme ve granülasyon izlendi. Makroskopik olarak yara boyutunda küçülme, epitelizasyon ve granülasyon birinci grupta ve ikinci grupta belirlendi. Mikroskopik olarak fibroblast sayısı, kollojen sentezi ve angiogenezisin, grup I'de grup 2 ile karşılaştırıldığında anlamlı olarak arttığı görüldü.

**TARTIŞMA:** Bu klinik çalışmada asit boriğin hem geniş spektrumlu antimikrobik özelliği, hem de yara iyileşmesinden sorumlu olan hücrelere pozitif etkisi gümüş nitratlı süngerlere kıyaslandığında alternatif olabileceği görüldü. Asit borikli süngerlerin NPWT sistemi ile kombine edilerek kullanılması travmaya bağlı açık yara iyileşmesinde iyi bir alternatif bir yöntem olabilir.

**Anahtar sözcükler:** Borik asit parçacıkları; borlu sünger; negatif basınçlı yara tedavisi.

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