


Negative pressure wound therapy for skin necrosis prevention after snakebite in the emergency department

A retrospective cohort study

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Abstract

This retrospective cohort study aimed to compare the effectiveness of conventional treatment and ultra-early application of negative pressure wound therapy (NPWT) in patients with snakebites.

Patients who visited the emergency department within 24 hours after a snakebite were assigned to the non- NPWT or NPWT group. Swelling resolution time and rates of necrosis, infection, and operations were compared between the 2 groups. The Stony Brook Scar Evaluation Scale was used to measure short- and long-term wound healing results.

Among the included 61 patients, the swelling resolution time was significantly shorter in the NPWT group than in non- NPWT group ($P = .010$). The NPWT group showed lower necrosis (4.3% versus 36.8%; $P = .003$) and infection (13.2% and 4.3%; $P = .258$) rates than the non- NPWT group. The median Stony Brook Scar Evaluation Scale scores were higher in the NPWT group than in the non- NPWT group ($P < .001$).

These findings suggest that ultra-early application of NPWT reduces edema, promotes wound healing, and prevents necrosis in patients with snakebites.

Abbreviations: ED = emergency department, NPWT = negative pressure wound therapy, SBSSES = Stony Brook Scar Evaluation Scale.

Keywords: edema, negative pressure wound therapy, skin necrosis, snakebites, wound infection

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1. Introduction

Globally, snakebites affect 5.5 million people per year, around 94,000 of whom die.^[1] Snake venoms are typically classified as hemotoxins, neurotoxins, necrotoxins, cardiotoxins, and nephrotoxins according to the different effects exerted.^[2] Typically, snake venoms in Far East Asia do not severely affect the human body, and many victims experience mild to severe local symptoms, such as pain, swelling, and necrosis, at the bite area. In Korea, 192 to 621 people are bitten by snakes annually, and on average, 5 people die of snakebites.^[3] Venomous snakes in Korea are divided into 2 taxonomic families: Viperidae and Elapidae. The pit viper, which belongs to the Viperidae family, is the most common venomous snake in Korea and has a hemotoxic and necrotoxic venom, although myotoxic and neurotoxic variants of pit vipers do exist.^[2,4] Pit viper venom produces local symptoms, such as necrosis, due to hemotoxins and necrotoxins.^[5–7] The primary complaints of patients with snakebites are local symptoms, including pain, swelling, and necrosis, in the bite area, especially in appendages such as fingers. These symptoms are caused by necrotoxins that damage the soft tissue and skeletal muscle.^[8] Necrotoxin-induced damage can lead to functional and aesthetic complications and may result in disability. Many studies have investigated the treatment of venomous snakebites and systemic complications,^[1,2,9] but few studies have examined local complications and active site treatments, especially in the emergency department (ED).^[10,11]

Negative pressure wound therapy (NPWT) is a simple and efficient treatment to promote healing in a variety of complicated wounds.^[12] NPWT, also called vacuum-assisted wound closure, refers to wound dressing systems that continuously or intermit-

tently apply subatmospheric pressure to the wound, resulting in the application of negative pressure to the surface of a wound, and the placing of a porous dressing in direct contact with the wound, with a drain attached to the vacuum device.^[13] NPWT has become a popular treatment modality for the management of many acute and chronic wounds and has been postulated to modulate the inflammatory response caused by soluble factors, such as inflammatory cytokines, collagenases, and elastases, and to accelerate the reduction in local inflammation.^[14]

The effects of NPWT on healing are attributable to primary and secondary mechanisms. The primary mechanisms include macro- and micro-deformation of the wound, tissue fluid removal, and changes in the wound environment, and the secondary mechanisms include hemostasis, inflammation control, cellular responses (eg, division, migration, and angiogenesis), formation of granulation tissues, peripheral nerve reactions, and decreased bioburden. NPWT improves regional blood flow and reduces bacterial proliferation, thereby limiting the opportunity for infection. At the cellular level, NPWT facilitates collagen synthesis, angiogenesis, and formation of granulation tissues.^[15–17] Moreover, conventional wound dressing changes must be frequently undertaken, whereas NPWT requires a dressing change every 48 to 72 hours, thus reducing clinical staff workload.^[13]

A complementary model, wherein many elements of wound healing are more clearly delineated, has recently been presented; in this model, the wound healing process is divided into 2 main stages: the early phase and the cellular phase. The early phase occurs within the first 24 hours after injury and is followed by the cellular phase.^[18] We hypothesized that the application of NPWT as early as possible in the ED would promote wound healing and prevent necrosis in snakebite wounds; we defined ultra-early application of NPWT as an application of NPWT within 24 hours after a snakebite. Accordingly, this retrospective cohort study aimed to determine the effects of ultra-early application of NPWT on snakebites by retrospectively comparing the incidence of necrosis and wound healing quality between patients who did and did not receive NPWT.

2. Methods

2.1. Study design and setting

This retrospective study included victims of snakebites who visited the ED of Chungnam National University Hospital, a university-affiliated 1365-bed care referral center in Daejeon, Korea, from March 2015 to February 2020. Hospital admission criteria were defined as follows: snakebite injury and symptoms such as hemorrhagic bullae, swelling, and necrosis. During the study period, the management of patients with snakebites changed from conventional methods to ones that included adjunctive NPWT. In detail, conventional treatment methods were used for patients who visited the ED from March 2015 to June 2018, and NPWT was added as a treatment method for patients who visited from July 2018 to February 2020. The effects of this transition on wound healing outcomes were analyzed. This study was approved by the Institutional Review Board (CNUH 2019–12-034).

2.2. Participants

The inclusion criteria for this study were:

- (1) a confirmed diagnosis of envenomation from a snakebite within 24 hours;

- (2) progressive worsening of the swelling extremity; local effect scores were used to evaluate swelling and ecchymosis, and patients with a total score ≥ 3 in both categories were included^[19]; and
- (3) the presence of hemorrhagic bullae.

The exclusion criteria were:

- (1) persons who had a mental illness diagnosed according to the ICD-10 criteria or those who did not cooperate with treatment even if not diagnosed with any mental illness;
- (2) currently breastfeeding or pregnant;
- (3) refusal of hospitalization; and
- (4) patients with mild symptoms (eg, patients with fang wounds, but without swelling, bullae, or necrosis).

2.3. Variables, data sources and quantitative variables

Wound cleaning and dressing were performed for all patients with snakebites who visited the ED during the study period. Conventional treatment was administered to all patients with snakebites who visited the ED from March 2015 through June 2018. These patients, classified as the non-NPWT group, received wound dressing, splint fixation, an antivenom injection, a tetanus antitoxin injection, antibiotics, fluid-replacement therapy, and bullae removal. All patients with snakebites were treated with 6000 IU of antivenom *Agkistrodon* within 1 hour of ED visit.

From July 2018 until February 2020, all eligible patients with snakebites received NPWT, in addition to conventional treatments (NPWT group), within 24 hours after being bitten. CuraVAC (CGbio, Seongnam-si, Korea) was used for applying NPWT in accordance with standard treatment protocols, with a negative pressure of 125 mm Hg maintained in continuous mode. The sponge replacement cycle was 72 hours, and maintenance of NPWT was undertaken every 72 hours.

The primary outcome was the presence or absence of necrosis; the secondary outcome was wound healing quality, evaluated using the Stony Brook Scar Evaluation Scale (SBSES). The SBSES is designed for short-term evaluation of scarring within 5 to 10 days following stitch removal, and it evaluates the width, height, and color of the wound, along with suturing marks and overall appearance; the scale grades each assessment item with a score of 0 or 1, with a total score ranging from 0 (very poor) to 5 (very good).^[20–22] Total SBSES scores of 0–3 are considered poor outcomes, whereas scores of 4 and 5 are considered good outcomes.

All wound follow-ups were conducted in accordance with the institutional wound-evaluation protocol of the study center. Short- and long-term follow-up periods were defined as 7 days and 6 months, respectively, and wound healing status was measured at each follow-up point using the SBSES. Scoring evaluations are shown in Table 1. In addition, both the infection rate and surgical intervention rate were recorded. In patients requiring surgery, a skin flap was used to cover the skin defect. Wound infection was defined as swelling with a focal rise in temperature and fever.^[23] Necrosis was defined as appearance of the necrotic tissue on the wound bed after treatment.^[24] Hospitalized patients were directly evaluated on the 7th day, and after being discharged, they were subsequently evaluated in the outpatient clinic at the Department of Plastic Surgery. A 6-month follow-up evaluation was undertaken in the outpatient clinic of the Department of Plastic

Scar category	Points
Width	
>2mm	0
≤2 mm	1
Height	
Elevated/depressed in relation to surrounding skin	0
Flat	1
Color	
Darker than surrounding skin	0
Same color or lighter than surrounding skin	1
Hatch marks/Suture marks	
Present	0
Absent	1
Overall appearance	
Poor	0
Good	1

The scale incorporates assessments of individual attributes using a binary response (1 or 0) for each variable, as well as overall appearance, to yield a score ranging from 0 (worst) to 5 (best).

Surgery. Except for the 7-day and 6-month follow-ups, additional follow-ups were performed as needed, depending on wound conditions. All study participants were evaluated by the same physician.

2.4. Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics, version 19 (IBM Corp., Armonk, NY), and the 2 study groups were compared. The Fisher exact test was used for the analysis of nominal variables, which are expressed as frequencies (percentages). Continuous variables were tested for normal distributions using the Shapiro–Wilk test. Non-normally distributed variables are expressed as median values (interquartile ranges), whereas normally distributed variables are described as means (\pm standard deviations). The Student *t*-test was applied for normally distributed data analyses, whereas the non-parametric Mann–Whitney *U*-test was used for non-normally distributed data analyses. The Wilcoxon signed-rank test was used to compare the SBSES scores of the short- and long-term results. *P*-values (*P*) < .05 were considered statistically significant for all analyses.

3. Results

3.1. Participants and descriptive data

Eighty-one patients with snakebite envenomation visited the ED of Chungnam National University Hospital between March 2015 and February 2020. Based on the study eligibility criteria, 20 patients were excluded, and a total of 61 patients were enrolled (Fig. 1). No statistically significant differences in age, sex ratio, location of injury, admission time after injury, and initial wound

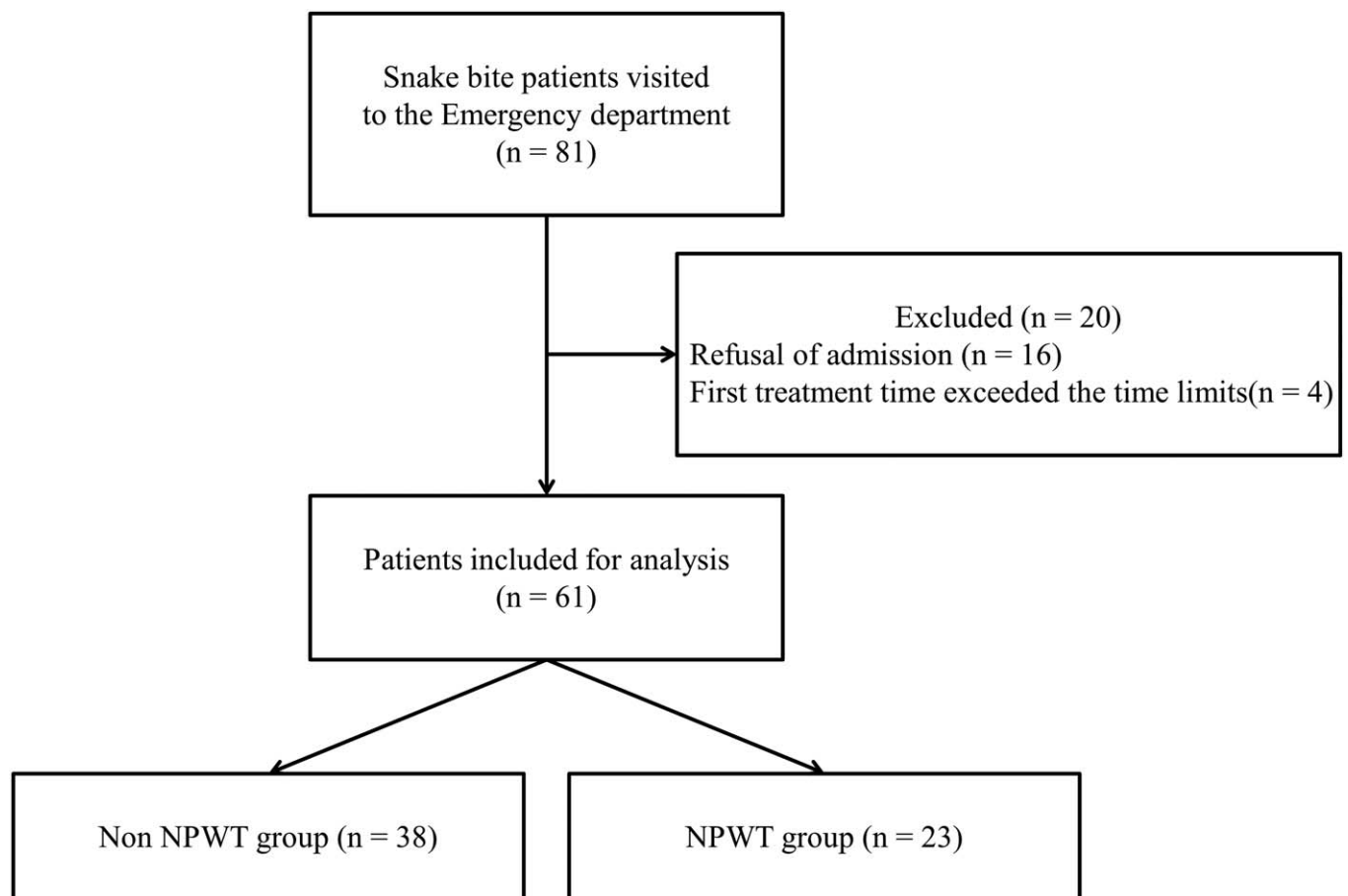


Figure 1. Flow diagram of patient enrollment. A total of 61 patients were enrolled; 38 patients underwent conventional treatment, and 23 received ultra-early NPWT. NPWT, negative pressure wound therapy.

Table 2
General characteristics, blood test results, and initial wound status of enrolled patients.

	Cohort (n=61)	Non-NPWT (n=38)	NPWT (n=23)	P-values
Male, n (%)	36 (59.0)	21 (55.2)	15 (65.2)	.592
Age, yr median (IQR)	61 (56–71)	60 (53.7–69.5)	66 (58.0–73.0)	.198
Past medical history				
Hypertension, n (%)	16 (26)	9 (23.6)	7 (30.4)	.765
Diabetes, n (%)	3 (5)	0 (0)	3 (13.0)	.049
Chronic renal disease, n (%)	1 (2)	1 (2.6)	0 (0)	1.00
Initial laboratory results				
WBC, x1000/ul, mean (SD)	8.218 (2.684)	8.059 (2.821)	8.480 (2.480)	.413
Hb, g/dl, mean (SD)	13.80 (1.51)	13.40 (1.41)	14.30 (1.54)	.022
NLR, ratio, median (IQR)	2.75 (1.55–4.37)	2.31 (1.28–3.84)	3.94 (1.74–4.91)	.113
CRP, mg/dL, median (IQR)	0.5 (0.5–0.6)	0.5 (0.5–0.5)	0.5 (0.5–0.8)	< .05
BUN, mg/dL, median (IQR)	16 (13–20)	17 (13.2–21)	15 (13–18)	.122
Cr, mg/dL, median (IQR)	0.76 (0.67–0.93)	0.76 (0.58–0.93)	0.76 (0.70–0.94)	.414
INR, ratio, median (IQR)	0.98 (0.92–1.04)	1.00 (0.94–1.04)	0.98 (0.80–1.06)	.290
aPTT, sec, median (IQR)	28.7 (25.9–31.0)	29.2 (25.9–31.7)	28.2 (25.4–30.2)	.188
Antivenin injection time after injury, hr, median (IQR)	8.0 (4.0–17.0)	7.5 (4.0–14.6)	14 (4.0–20.0)	.179
Admission time after injury, hr, median (IQR)	10 (5–21.5)	9.0 (5.0–17.3)	17 (6.0–22.0)	.091
Initial wound status				
Location				
Finger, n (%)	40 (65.6)	27 (62.5)	13 (37.5)	.251
Palm, n (%)	2 (3.3)	1 (50)	1 (50)	.718
Foot, n (%)	14 (23)	8 (57.1)	6 (42.9)	.653
Other areas, n (%)	5 (8.2)	2 (40)	3 (60)	.287
Skin color change, n, (%)	18 (29.5)	9 (50)	9 (50)	.160

aPTT = activated partial thromboplastin time; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; Hb, hemoglobin; INR, international normalized ratio; IQR, interquartile range; NPWT, negative-pressure wound therapy; SD, standard deviation; WBC, white blood cell.

status were found between the 2 groups (Table 2). In the NPWT group, the median NPWT application time following a snakebite was 7 (4.0–16.0) hours. Blood tests revealed that the C-reactive protein and hemoglobin levels in both groups were normal (Table 2).

3.2. Primary results

The median duration to the resolution of swelling in the wound area was 4.0 (3.0–5.0) days and 3.0 (3.0–4.0) days in the non-NPWT and NPWT groups, respectively, a statistically significant difference ($P = .010$; Table 3). Three surgeries were performed in

the non-NPWT group, whereas none were performed in the NPWT group; however, this difference was not statistically significant ($P = .234$; Table 3). Necrosis rates were 36.8% and 4.3% in the non-NPWT and NPWT groups, respectively, and this difference was significant ($P = .003$; Table 3). There were 12 cases of necrosis and 1 case of finger necrosis in the non-NPWT and NPWT groups, respectively. In addition, patients in the non-NPWT group showed extensive necrosis that required surgery, whereas patients in the NPWT group experienced focal necrosis (Fig. 2). The infection rates were 13.2% and 4.3% in the non-NPWT and NPWT groups, respectively, a not statistically significant difference ($P = .258$; Table 3).

Table 3
Treatment results in the 2 study groups.

	Cohort (n=61)	Non-NPWT (n=38)	NPWT (n=23)	Relative risk (95% CI)	P-values
Swelling full resolution time, day, median (IQR)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	3.0 (3.0–4.0)		.010
Necrosis, n (%)	15 (24.6)	14 (93.3)	1 (6.7)	0.660 (0.510–0.885)	.003
Finger, n (%)	13 (21.3)	12 (92.3)	1 (7.7)	0.602 (0.415–0.873)	.013
Palm, n (%)	0 (0)	0 (0)	0 (0)		0
Foot, n (%)	2 (3.3)	2 (100)	0 (0)	0.750 (0.503–1.119)	.202
Other areas, n (%)	0 (0)	0 (0)	0 (0)		0
Infection, n (%)	6 (9.8)	5 (83.3)	1 (16.7)	0.908 (0.780–1.056)	.258
Initial skin color change					.160
Yes, n (%)	18 (29.5)	9 (50)	9 (50)		
Necrosis, n (%)		5 (27.8)	1 (5.6)	0.500 (0.232–1.076)	.046
No, n (%)	43 (70.5)	29 (67.4)	14 (32.6)		
Necrosis, n (%)		9 (20.9)	0 (0)	0.690 (0.540–0.880)	.019
Operation, n (%)	3 (4.9)	3 (100)	0 (0)	0.921 (0.893–1.011)	.234

CI = confidence interval; NPWT = negative pressure wound therapy.



Figure 2. A) A 66-year-old female patient with a snakebite on her left thumb. (A) Traditional treatment. (B) After 15 days, there was progression of necrosis, including hemorrhagic bullae at the bite site. (C) Wound debridement followed by a skin flap graft. (D) After 2 months, the skin defect persisted. B) A 51-year-old man presented with a snakebite on the right little finger. (A) Skin color changes and hemorrhagic bullae were observed during examination in the emergency department. (B) Wound debridement was undertaken. (C) The patient received ultra-early NPWT. (D) On day 3 of hospitalization, the wound healed without necrosis. C) A 61-year-old man with a snakebite on the right fourth finger. (A) A large hemorrhagic bulla and skin color changes were identified during the visit at the emergency department. (B) Removal of hemorrhagic bullae and wound debridement was undertaken. Ultra-early NPWT was applied, and the patient was discharged 3 days later. (C) Outpatient follow-up after 24 days. (D) At the 6-month follow-up, the patient completely recovered without complications. NPWT, negative pressure wound therapy.

3.3. Outcome data

In short- and long-term follow-up evaluations, the median SBSES scores were 4 (3.75–4) and 3 (2.75–3) in the non-NPWT group and 4 (4–5) and 5 (5–5) in the NPWT group ($P < .001$), respectively (Fig. 3). In particular, the median SBSES scores in the long-term follow-up evaluation were lower in the non-NPWT group than in the NPWT group ($P < .001$; Fig. 3).

4. Discussion

In this retrospective study, the NPWT group showed marked decreases in necrosis and time to resolution of swelling, and better cosmetic results than the non-NPWT group. The NPWT group had a higher SBSES score than the non-NPWT group. In particular, the non-NPWT group showed a statistically significant decrease in median SBSES scores, from 4 (3.75–4) to 3 (2.75–4), in the long-term follow-up evaluation than in the short-term follow-up evaluation. Therefore, the non-NPWT group exhibited poorer outcomes than the NPWT group, probably because the ultra-early application of NPWT reduces the wound extent through negative pressure and increases blood flow, which aids wound recovery.^[25] In addition, worsening of wounds in the non-NPWT group might be attributable to failed prevention of the progression of necrosis in the ultra-early stages (Fig. 2).

4.1. Interpretations

Snake venoms contain both enzymatic and non-enzymatic proteins, the latter being primarily responsible for the poisoning effects. Following a snakebite, toxins are injected into the body, and local symptoms, such as burning pain, occur within minutes. Pit viper venom produces more local than systemic symptoms due to hemotoxins and necrotoxins.^[5] Edema and rashes develop within hours, and swelling becomes severe. Hemorrhagic plaques and bullae develop, and if not properly treated, severe tissue necrosis can occur. Moreover, effects on the lymphatic system are common and may include lymphadenitis and lymphadenopathy, which can lead to serious complications.^[26] Therefore, initial treatment in the ED is critically important when treating snakebites. Snakebite treatments involve general wound management, such as irrigation, gauze dressing, and removal of hemorrhagic bullae. However, conventional treatment may lead to long recovery time and poor functional and cosmetic results because of the effects of necrotoxins, which cause skin and soft tissue necrosis. In many cases, the skin or soft tissue defect site needs to be reconstructed through skin transplantation and flap surgery.^[26] The bullae formed by the snakebite are filled with toxins and can function as a venous depot inaccessible to the antivenom, and are subsequently able to release it.^[27] Accordingly, it is important to remove hemorrhagic bullae and facilitate

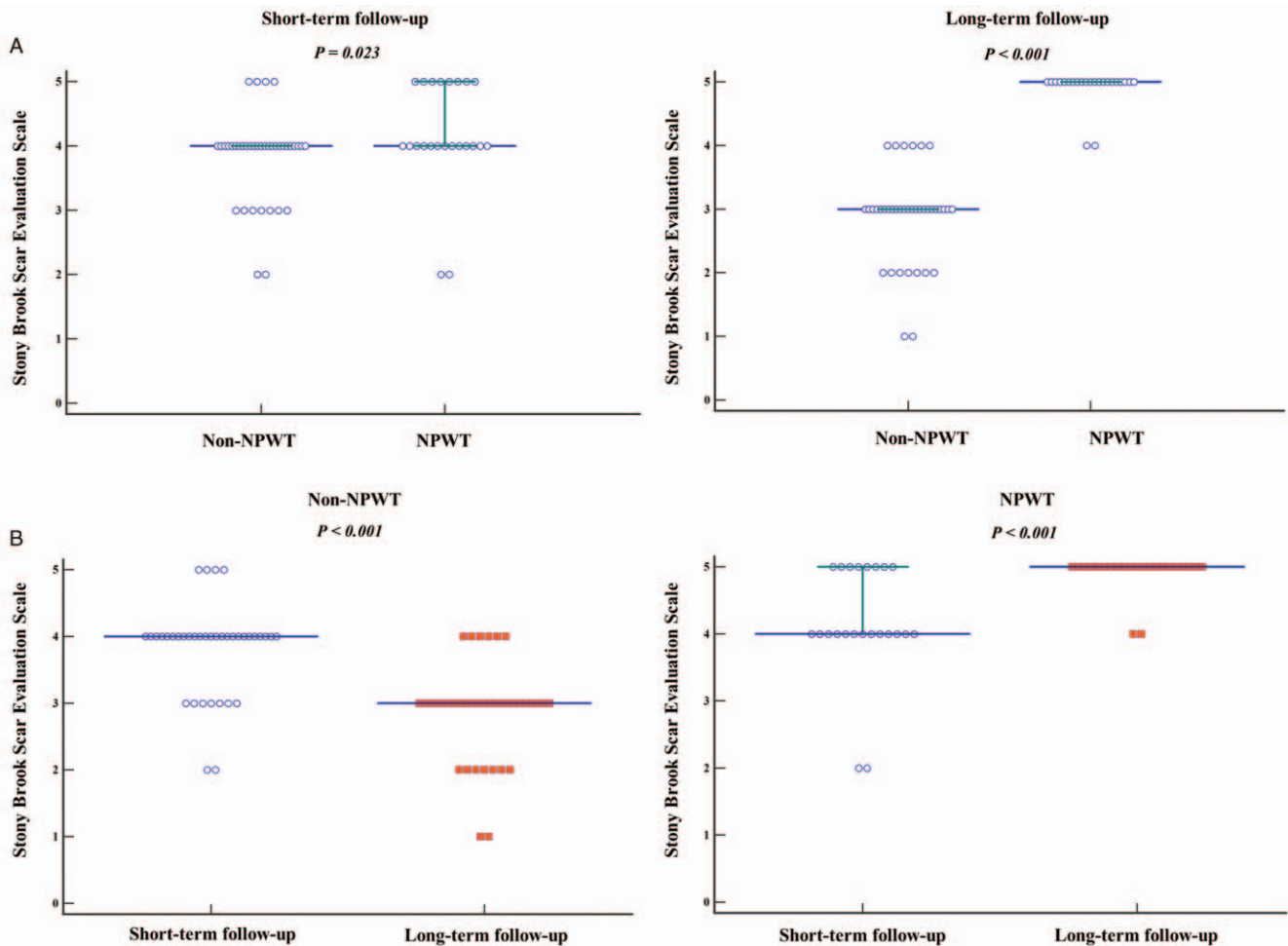


Figure 3. A) Comparison of the Stony Brook Scar Evaluation Scale results between Non-NPWT and NPWT groups using the Mann–Whitney *U*-test. Solid lines indicate the median values with interquartile ranges. B) Comparison of the Stony Brook Scar Evaluation Scale between short and long-term follow-up evaluations for each group using the Wilcoxon signed-rank test. Solid lines indicate median values with interquartile ranges. Circles indicate the short-term follow-up outcomes, whereas squares indicate long-term follow-up outcomes based on the scores of the scar evaluation scale. NPWT, negative pressure wound therapy.

blood circulation and wound recovery in the bite area.^[5,28] However, removal of hemorrhagic bullae alone may not fully lead to wound healing in patients with snakebites, and additional treatment, such as NPWT, is necessary in the ED.

NPWT clinically enhances wound vascular perfusion, formation of granulation tissue, and removal of germs and is associated with increased survival after flap and skin transplantation; in addition, it reduces edema or compartment syndrome due to burns, crush injuries, and necrotizing wounds.^[12,13] In patients with snakebites, NPWT may induce toxin entrapment, thereby preventing the necrotoxin from spreading further into the wound; it has been thought that the effect occurs only focally by preventing the necrotoxin from diffusing into the surrounding tissues. Therefore, natural healing can be promoted by sequestering the toxin at the necrotic site. Moreover, NPWT can promote wound healing through the regulation of cytokines or anti-inflammatory profiles and by mechanoreceptor- and chemoreceptor-mediated cell signaling, angiogenesis, extracellular matrix remodeling, and the formation of granulation tissue.^[29] In addition, mitochondria are the primary location for cellular respiration, and overexpression of mitochondrial

antioxidant manganese superoxide dismutase prevents cell death caused by oxidative stimulation.^[30–32] In a recent study, using patient samples and rodent models of acute injury, significant accumulation of mitochondrial antioxidant manganese superoxide dismutase, as well as higher enzymatic activity, was observed in tissues in the NPWT group, and the underlying mechanism is thought to be related to reduced necrosis.^[33] Therefore, NPWT can help reduce edema, necrosis, and infection in the distal end of the fingers, which receive less blood flow.

Some studies have demonstrated that NPWT appears safe and effective in managing acute, contaminated wounds in patients meeting sepsis criteria.^[34] The clinical efficacy and cost-effectiveness of NPWT have been extensively investigated in several randomized controlled trials and meta-analyses,^[35,36] and NPWT has been widely accepted for the treatment of open and infected wounds and for accelerated treatments in many clinics. A previous study found that the application of multiple, small incisions combined with NPWT on the incision sites was effective in controlling the release of inflammatory cytokines and alleviating systemic inflammatory reactions.^[37] However, that study only investigated the effects of NPWT on swelling and

inflammation but did not specifically examine wound healing and skin necrosis. In the present study, 2 groups of patients with snakebites were analyzed: those who underwent basic, conventional treatment procedures and those who received additional negative pressure therapy within 24 hours after snake bites. We found that necrosis and time to swelling resolution were reduced in the NPWT group. It is thought that by increasing blood flow through negative pressure, nutrients are supplied to areas with circulatory disruption, such as edema. In addition, NPWT may help heal wounds by preventing blood retention or venous and lymphatic fluid retention through the direct influence or extravasation of the venom.^[38] Ultra-early application of NPWT resulted in the effective removal of tertiary fluids and debris, thus reducing swelling and necrosis.

4.2. Limitations

This study has some limitations. First, the present study was a single-center study, and the number of study participants was relatively small. Second, this was a retrospective study; thus, it is difficult to fully demonstrate the effectiveness of NPWT in snakebite wounds. Therefore, further multicenter, prospective studies are needed to decisively demonstrate the effects of the ultra-early application of NPWT in snakebite patients.

5. Conclusions

This study found that the ultra-early application of NPWT reduced edema, promoted wound healing, and prevented necrosis in patients with snakebites. The findings demonstrate the high effectiveness of the ultra-early application of NPWT in patients with snake bites. Accordingly, we recommend NPWT application in patients with snakebites in the ED setting as soon as possible to promote wound healing and prevent necrosis.

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