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Original Article

Effects of topical oxygen therapy on chronic traumatic wounds and its impact on granulation tissue

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Abstract: Objective: To evaluate the effects of topical oxygen therapy and its impacts on granulation tissue in patients with chronic traumatic wounds. Method: A total of 112 patients with chronic traumatic wounds were randomly divided into the control group (n=56, receiving negative-pressure wound therapy) and the intervention group (n=56, receiving negative-pressure wound therapy plus topical oxygen therapy) using a random number table and they were treated continuously for 2 weeks. Then, the scores from the Pressure Ulcer Scale for Healing (PUSH), the coverage rate of granulation tissue, the severity of pain and Transcutaneous Oxygen Partial Pressure ($TcPO_2$) before and after treatment were compared between the two groups. Also, the bacterial culture-positive rate, the healing rate and the healing time were compared between the two groups. Results: The PUSH scores were significantly decreased after treatment compated to those before treatment in the two groups, and those in the intervention group were lower than those in the control group (all $P<0.05$). The coverage rate of granulation tissue gradually increased in the two groups from day 3 to day 14 after treatment, with that in the intervention group being higher than in the control group during the same period (all $P<0.05$). The bacterial culture-positive rate that was detected was significantly lower after treatment than that before treatment in the intervention group, and lower in the intervention group than in the control group after treatment (all $P<0.05$). The VAS scores significantly decreased and $TcPO_2$ increased after treatment compared to those before treatment in the two groups, with changes in the intervention group being more significant than those in the control group (all $P<0.05$). During the 3-month follow-up, the wound healing rate was higher and the healing time shorter in the intervention group than those in the control group (all $P<0.05$). Conclusion: Negative-pressure wound therapy plus topical oxygen therapy can substantially increase the coverage rate of granulation tissue and $TcPO_2$ at the traumatic site, thus facilitating the healing process and shortening the time for healing. So, the efficacy of negative-pressure wound therapy in combination with topical oxygen therapy is more effective in treating patients with chronic traumatic wounds than negative-pressure wound therapy alone.

Keywords: Chronic traumatic wounds, topical oxygen therapy, efficacy, granulation tissue

Introduction

Chronic traumatic wounding is a trauma-induced type of skin damage that persists for over 1 month. It is difficult to handle in clinical treatment and can lead to repeated ulcers if treated improperly, seriously affecting the daily life and work of patients [1, 2]. Negative-pressure wound therapy, which shortens the time for healing by facilitating the tissue growth and accelerating angiogenesis at the wound site, is commonly used in the treatment of acute and chronic traumatic wounds. However, it creates a negative-pressure environment by withdrawing oxygen within the wound tissue, which may result in anaerobic infection and affect the healing process [3-5]. Therefore, it is proposed that negative-pressure wound therapy combined with topical oxygen therapy can theoretically decrease the occurrence of anaerobic infection at the wound site, thus facilitating the healing process [6].

Topical oxygen therapy was firstly proposed by Professor Sen from the Comprehensive Wound Center for Surgery, at Ohio State University Medical Center, USA, who proved that topical oxygen therapy was a treatment that could supply sufficient oxygen to the superficial tissue at the wound site so as to compensate the hypoxic

condition. It is a convenient and safe therapy that accelerates the wound healing process [7]. In this research, patients with chronic traumatic wounds were selected as research subjects to investigate the effects of negative-pressure wound therapy combined with topical oxygen therapy on their wound healing process and the growth of granulation tissue. The results are reported as follows.

Materials and methods

General data

A total of 112 patients with chronic traumatic wounds who were admitted to our hospital from December 2018 to February 2020 were selected prospectively and were randomized into the control group (n=56, receiving negative-pressure wound therapy) and the intervention group (n=56, receiving negative-pressure wound therapy plus topical oxygen therapy) using a random number table method. Patients were eligible if they had marked traumatic wounds which persisted over a month; the length of their wound was greater than 5 cm or the area larger than 5 cm^2; and they were cooperative during this research. Patients were excluded if they had diabetes; the wound bleed at the wound site while moving; they had visible major blood vessels or nerves; they had blood coagulation disorders; they had malignant tumors; they were mentally ill; or they were pregnant or breast feeding. All patients provided written informed consent, and this study was approved by the Ethics Committee of our hospital.

Methods

Patients were treated routinely after admission, including disinfection, removal of necrotic tissues and antibiotics to prevent infection. Then, patients in the control group were treated with negative-pressure wound therapy [8] alone with the use of an intelligent negative-pressure wound therapy comprehensive instrument purchased from Shandong Chuangkang Biotechnology Co., Ltd. (China), which was set on intermittent vacuum sealing mode with -120 mmHg pressure and used intermittently each day for 2 weeks, with 3 min for each vacuuming event and 1 min of rest interval. Patients in the intervention group were given topical oxygen therapy on the basis of negative-pressure wound therapy with the use of a micro-oxygen therapy instrument purchased from Zhengzhou Runyuan Medical Instrument Co., Ltd. (China) [9]. The parameters were set as follows: oxygen flow rate was 3 L/min, temperature was between 27°C and 28°C, humidity was 65%. Oxygen was given constantly each day for 2 weeks. The oxygen-delivering tube and vacuuming tube were both wrapped with gauze and the wound was sealed using transparent sticky film.

Outcome measures

Primary outcome measures: The wound was scored using the PUSH Tool before treatment as well as after treatment, which includes exudate volume within 24 hours (3 points), pressure ulcer area (10 points) and the type of wound tissue 4 points, including sealed tissue (0 points), epithelial tissue (2 points), granulation tissue (3 points), slough (4 points) and necrotic tissue (5 points), with less exudate volume within 24 hours and lower scores for pressure ulcer area indicating better healing of the wound [10].

Coverage rate of the granulation tissue: the areas of wound and granulation tissue were measured using a ruler during each dressing. The coverage rate of granulation tissue equals to the granulation tissue area/total wound area *100%.

Secondary outcome measures: After treatment, a sterile cotton swab was dipped in the exudates for the culture and identification of bacteria strains. The cultured positive rate of bacteria equals to the number of identified bacterial strains/total bacterial strains *100%.

Degree of pain and $TcPO_2$: the degree of pain was evaluated by the VAS Tool before and after treatment using a vernier ruler of about 10 cm in length, with 10 tick marks on one side and “0” and “10” at both ends, respectively [11]. Zero indicating no pain and ten indicating intolerable pain; $TcPO_2$ was measured by a transcutaneous oxygen partial pressure measuring instrument.

Patients were followed up for 3 months. The healing rate and the healing time were compared between the two groups. The criteria to assess the wound healing situation were whether the wound was covered with epithelial tissue and whether the result of an oxidation reaction with 3% hydrogen peroxide was nega-

Table 1. Comparison of Baseline Data between the two groups (n, $\bar{x} \pm sd$)

Measures	Intervention group (n=56)	Control group (n=56)	χ^2/t	*P*
Sex (n)			0.583	0.445
Male	30	34		
Female	26	22		
Age (year)	43.3±5.4	41.9±6.2	1.274	0.205
BMI (kg/m^2)	23.02±1.88	22.87±1.59	0.456	0.649
Wound type (n)			2.683	0.443
Traumatic soft tissue defect	30	25		
Open fracture with infection	13	19		
Post-operative infection and wound separation	6	8		
Others	7	4		
Duration of the wound (d)	42.2±5.3	43.8±4.7	1.690	0.094
Length of the wound (cm)	7.56±2.05	7.79±1.98	0.604	0.547
Wound area (cm^2)	6.85±1.04	7.02±1.22	0.794	0.429
PH of the wound exudates	8.05±0.55	8.17±0.49	1.219	0.225

Note: BMI: Body Mass Index.

Table 2. The scores of all items in PUSH in the two groups before and after treatment ($\bar{x} \pm sd$)

Group	Time	Wound exudate volume within 24 hours	Pressure ulcer area	Type of the wound tissue
Intervention group (n=56)	Before treatment	2.33±0.44	7.28±1.05	3.32±0.54
	After treatment	1.26±0.40$^{*,\#}$	2.84±1.08$^{*,\#}$	1.39±0.49$^{*,\#}$
Control group (n=56)	Before treatment	2.39±0.50	7.84±1.36	3.36±0.44
	After treatment	1.70±0.42*	4.70±1.29*	2.11±0.40*

Note: Compared with that before treatment, *P<0.05; compared with the control group, $^{\#}$P<0.05.

tive. The healing rate equals to the number of patients with healed wounds/the total number of patients *100%.

Statistical analysis

SPSS 20.0 was used for data analyses. Enumeration data were expressed as n (%), and χ^2 test was used for comparison. Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm sd$). Paired t test was used for comparison between the same group before and after treatment. Independent sample t test was used for between-group comparison. P<0.05 was considered statistically significant.

Results

Baseline data

There was no significant difference in the baseline data in the two groups and the data were comparable (all P>0.05). See **Table 1**.

Wound healing (PUSH)

The scores of exudate volume within 24 hours, pressure ulcer area, type of the wound tissue were all significantly decreased after treatment than those before treatment in the two groups, with those in the intervention group being lower than those in the control group (all P<0.05). See **Table 2**.

Coverage rate of the granulation tissue

Coverage rate of the granulation tissue had gradually increased in the two groups from day 3 to day 14 after treatment, with that in the intervention group being higher than that in the control group during the same period (all P<0.05). See **Table 3**.

Culture-positive rate

There was no significant difference in the culture-positive rate detected in the bacteria strains from the wound exudate in the two

Table 3. Coverage rate of the granulation tissue in the two groups during treatment ($\bar{x}$ ± sd)

Group	Day 3	Day 6	Day 9	Day 12	Day 14
Intervention group (n=56)	10.40±1.94#	19.95±3.38#	34.48±4.30#	43.50±3.98#	56.59±4.57#
Control group (n=56)	8.88±1.73	15.50±3.74	30.03±3.85	38.88±4.47	44.40±4.70

Note: Compared with the control group, #P<0.05.

Table 4. Comparison of the culture-positive bacterial rate between the two groups (n, %)

Group	Time	Staphylococcus aureus	Pseudomonas aeruginosa	Escherichia coli	Other bacteria	Total
Intervention group (n=56)	Before treatment	8 (14.29)	4 (7.14)	2 (3.57)	2 (3.57)	16 (28.57)
	After treatment	3 (5.36)	2 (3.57)	1 (1.79)	0 (0.00)	6 (10.71)*,#
Control group (n=56)	Before treatment	9 (16.07)	5 (8.93)	2 (3.57)	2 (3.57)	18 (32.14)
	After treatment	7 (12.50)	3 (5.36)	3 (5.36)	2 (3.57)	15 (26.79)

Note: Compared with that before surgery, *P<0.05; compared with the control group, #P<0.05.

Table 5. Comparison of VAS scores of the degree of pain and $TcPO_2$ in the two groups (%, $\bar{x}$ ± sd)

Group	Time	VAS scores (point)	$TcPO_2$ (%)
Intervention group (n=56)	Before treatment	6.69±1.94	33.75±4.40
	After treatment	2.20±0.74*,#	56.68±6.59*,#
Control group (n=56)	Before treatment	6.48±1.82	34.04±5.33
	After treatment	3.97±1.13*	43.08±5.40*

Note: Compared with that before treatment, *P<0.05; compared with the control group, #P<0.05.

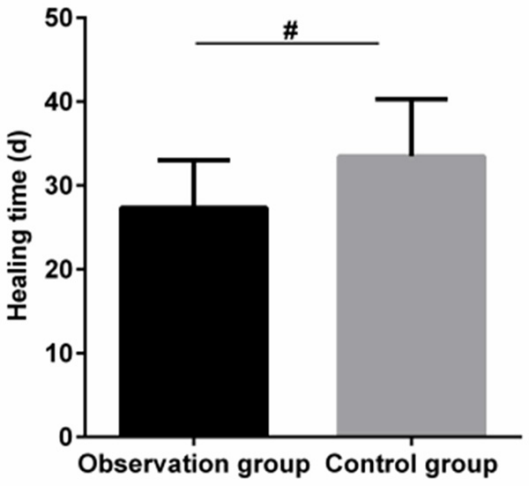

Figure 1. Comparison of wound healing time between the two groups. Compared with the control group, #P<0.05.

groups before treatment (all P>0.05). However, the culture-positive rate after treatment was markedly lower in the intervention group than in the control group and also significantly lower than that before treatment in the intervention group (all P<0.05). See **Table 4**.

Degree of the pain and $TcPO_2$

There was no significant difference in VAS scores and $TcPO_2$ between the two groups before treatment (all P>0.05). However, the VAS scores were declined and $TcPO_2$ was elevated in the two groups after treatment as compared with those before treatment, with more substantial changes observed in the intervention group than those in the control group (all P<0.05). See **Table 5**.

Wound healing rate and healing time

During the 3-month follow-up, the wound healing rate was 89.29% (50/56) in the intervention group, which was significantly higher than 73.21% (41/56) in the control group, and the time needed for healing was markedly shorter in the intervention group ((27.34±5.68) d) than that in the control group ((33.47±6.83) d) (all P<0.05). See **Figure 1**.

Discussion

Negative-pressure wound therapy has undeniable advantages in wound healing, such as effectively promoting tissue proliferation, accelerating angiogenesis at the traumatic site and shortening the time needed for healing [12]. However, some studies have reported that dur-

ing the wound repairing process, hydroxylase and collagen can only be combined in an environment with sufficient oxygen to produce pro-angiogenic hydroxylated collagen for accelerating the healing process [13, 14].

In our study, the PUSH scores of exudate volume within 24 hours, wound area and type of tissues were all lower after treatment in the intervention group than those in the control group. The coverage rate of granulation tissue from day 3 to day 14 was higher in the intervention group than that in the control group, suggesting negative-pressure wound therapy combined with topical oxygen therapy could markedly increase the granulation tissue coverage at the traumatic site in patients with chronic traumatic wounds, so as to facilitate the wound healing process. This result showed that the efficacy of the combined therapy was better than negative-pressure wound therapy alone, which is consistent with the study result of Tlapák et al., who also confirmed that negative-pressure wound therapy plus topical oxygen therapy was more conducive to the healing of chronic wounds [15]. The result of the 3-month follow-up showed that the healing rate was substantially higher in the intervention group than that in the control group (89.29% vs. 73.21%), and the healing time was markedly shorter in the intervention group than that in the control group ((27.34±5.68 d) vs. (33.47±6.83 d)), suggesting negative-pressure wound therapy plus topical oxygen therapy could significantly increase the healing rate and shorten the healing time so as to effectively facilitate the healing process of chronic traumatic wounds.

It is also reported that an appropriate amount of oxygen partial pressure is essential for wound healing, which can be facilitated with $TcPO_2$ maintained at 50~100 mmHg [16, 17]. Kimmel et al. studied the effects of different oxygen flow rates on wound healing, and found that the healing time could be greatly shortened when oxygen was given continuously at a rate of 2 to 3 L/min, with the $TcPO_2$ maintained at 45-80 mmHg [18]. Therefore, oxygen was given continuously at a rate of 3 L/min in our study. The result showed that $TcPO_2$ was higher and VAS scores were lower in the intervention group than those in the control group, suggesting negative-pressure wound therapy combined with topical oxygen therapy could substantially increase $TcPO_2$ at the traumatic site and reduce the degree of pain in patients with chronic traumatic wounds. This result is consistent with the result of Deng et al., who also found that topical oxygen therapy could promote wound healing process by increasing $TcPO_2$ at the traumatic site [19].

Staphylococcus aureus and pseudomonas aeruginosa are the main pathogens that result in extended wound area and protracted healing time [20, 21]. In our study, staphylococcus aureus, pseudomonas aeruginosa and escherichia coli etc. were all detected in the exudate of patients in the two groups before treatment. However, the culture-positive rate was markedly lower after treatment than that before treatment in the intervention group and also lower in the intervention group than that in the control group after treatment, indicating negative-pressure wound therapy combined with topical oxygen therapy could substantially decrease the number of bacteria at the traumatic area, which might be related to sufficient oxygen given during the negative-pressure wound therapy that had inhibited the growth as well as proliferation of the bacteria [22].

However, this is a single-center study with a small sample size and short-term follow-up. Therefore, further studies with larger simple sizes and longer follow-up periods should be designed to verify the effects of negative-pressure wound therapy combined with topical oxygen therapy in patients with chronic traumatic wounds.

In summary, negative-pressure wound therapy plus topical oxygen therapy can substantially increase the coverage rate of granulation tissue and $TcPO_2$ at the traumatic site, thus facilitating the healing process and shortening the healing time. Its efficacy is better than that of negative-pressure wound therapy alone.

Disclosure of conflict of interest

None.

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