Int J Clin Exp Med 2013;6(8):649-654
www.ijcem.com /ISSN:1940-5901/IJCEM1306013

Original Article

Clinical study on the treatment of chronic wound with negatively-charged aerosol

Xiaoxia Xie[1*], Lei Chen[1*], Zhao-Qiang Zhang[2], Yan Shi[1], Julin Xie[1]

[1]Department of Burn Surgery, First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong, China; [2]Department of Oral and Maxillofacial Surgery, Hospital of Stomatology, Guangzhou Medical University, 39 Huangsha Road, Liwan District, Guangzhou City, Guangdong Province, China. [*]Equal contributors.

Received June 16, 2013; Accepted July 1, 2013; Epub September 1, 2013; Published September 15, 2013

Abstract: Background: Aerosols are defined as the mixture of liquid or solid particles/droplets that are stably suspending in air. When carrying a certain amount of negative charge, they will be defined as negatively-charged aerosol. This report investigates the effect of negatively-charged aerosol on the healing of chronic wound. Methods: 140 patients with chronic wound were assigned randomly into two groups. Normal, routine treatment was applied on chronic wounds of 73 patients depending on wounds situation (control group). While another 67 similar patients received negatively-charged aerosol therapy (2 hours per time, twice a day) and were used as experimental group. Wound healing assessment including the patients' complication, detection of bacteria in wound secretions, and evaluation of wound healing. Results: The results of our study showed that after the application of negatively-charged aerosols, and condition and infection rate of wounds from experiment group were better and lower than that of control group. In comparison with control group, the relative size of wounds from experiment group was significantly smaller ($P<0.05$) at post-treatment day 0, 7, 14, 21 and 28. Also, the time required for wound healing in the experimental group was significantly shorter ($P<0.05$) than that in the control group. Conclusion: Negatively-charged aerosol therapy can accelerate wound healing speed and improve the healing of chronic wounds. Thus, we wound recommend the consideration of Negatively-charged aerosol therapies in addition to normal wound treatment in cases of chronic wound.

Keywords: Negatively-charged aerosol, healing, chronic wound

Introduction

Including venous stasis ulcerations, diabetic lower extremity ulcers, chronic wounds lead to a reduction in quality of life caused by pain and immobility, represent a serious medical and societal problem [1, 2]. The challenges brought up by chronic wounds are not only the economic costs of the adequate care of patients who must be treated for months or years, but also the limited therapeutic options for these wounds are associate with poor re-epithelialization, angiogenesis, granulation tissue formation and infection. There is an unmet need to develop a pertinent healing-promoting therapy.

Carrying a certain amount of negative charge, negatively-charged aerosols are defined as the mixture of liquid or solid particles/droplets that are stably suspending in air [3, 4]. The variety of their shapes, sizes, densities and electrical charge will affect particles' behavior. As reported by Kruger and his co-workers early in 1950s, negatively-charged aerosols can accelerate ciliary activity in the respiratory tract of experimental animal and human [5-9]. This change may lead to the improvement of air passages hygiene. Ever since its introduction to China in 1983, negatively-charged aerosols technology has become a focus of research for years. However, whilst a body of its application in the treatment of various diseases has been reported, it is not until 2005 that Xu YB and his co-workers reported a clinical trial concerning its utilization in burned wounds for the first time [10]. Started from 1998, their research team applied the first and second generation aerosol bioelectricity instruments sequentially to treat the burned wounds. After the evaluation of 280 patients with superficial to deep partial thick-

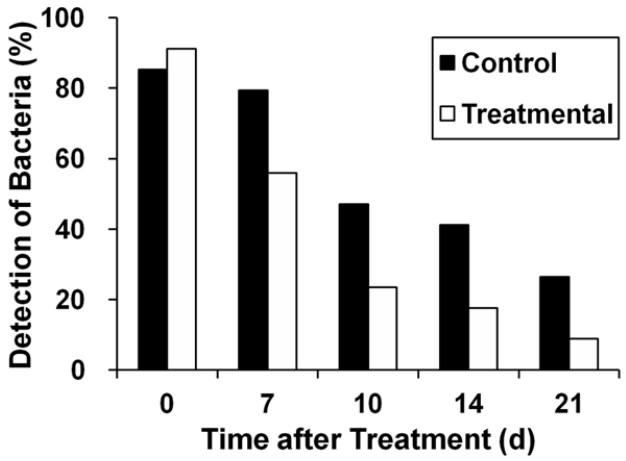

Figure 1. Wound secretions were collected at selected time points (post-treatment day 0, 10, 14, 21 and 28) and were used for bacterial culture, bacterial infection in two groups has no significant difference at day 0 ($P>0.05$). The difference of infection rate between two groups was significant ($P<0.05$) at all the selected time points.

ness burn, they concluded that negatively-charged aerosols are safe and effective in promoting wound healing of patients with partial thickness burned wounds. They also conducted some related studies by using burned animal models and suggested that the mechanisms associated with burned wound healing promotion are negatively-charged aerosols can up regulate the expression of PDGF1 and down regulate TNP expression which will collectively inhibit the inflammation reaction; 2) Promote IL-10 secretion and inhibit IL-8 synthesis during inflammation phase which will shorten the time needed for wound closure; 3) Promote and inhibit TGF-β1 expression on the early and late stage of wound healing respectively; 4) Promote the expressions of EGF, 1 integrin and K19 for accelerating the proliferation of epidermal stem cells.

The use of negatively-charged aerosols to control the spread of airborne infection has been previously discussed [11-13]. It has been widely reported that negatively-charged aerosols have apparent biocidal action that can inhibit the growth of Candida albicans [14], Staphylococcus albus [15], etc. Considering infection is one of the factors that detrimental to the healing of chronic wounds [16, 17], we suggest that negatively-charged aerosols may accelerate chronic wounds healing by controlling hospital infection acquirement and acting as bactericidal factors. In order to investigate the effect and the ideal therapeutic method of negative-charged aerosols on the healing process of chronic wounds, we therefore report a pilot study conducted by using negative-charged aerosols therapeutic apparatus. In this study we enrolled patients with chronic wounds located at different sites and caused by various reasons. Wound healing assessment including the patients' complication, detection of bacteria in wound secretions, and evaluation of wound healing. The outcomes from this study have validated a new therapeutic option for the promotion of chronic wound healing.

Materials and methods

Negative-charged aerosols therapeutic apparatus

Negative-charged aerosols therapeutic apparatus (**Figure 1**, SQ-365 aerosols apparatus, Siqi Electronic Equipment Co., Ltd. P. R. China) is a device that only provides a purely physical effect on the wound and does not contain any medicinally effective constituents. Aerosols generated by this therapeutic apparatus are with negative charges and the sizes of them are about 5 μm. They can form an aerosol cloud whose droplets have a density of 107/cm^3 (detected within 30 cm apart from the apparatus). These negative-charged, uniformed aerosols can bypass upper airway, mucosa and wound bed and directly enter the human body. When applied on wounds, these aerosols shall have a biocidal effect on wounds and can promote wound healing by affecting the cellular metabolism and activity of cells [10, 25].

Indications for use

Indications for the application of the negative-charged aerosols therapeutic apparatus are ulcer/wound does not heal after 4-week routine therapy. The included cases are patients with traumatic ulcer, compression ulcer, crural ulcers of venous, arterial or mixed genesis, diabetic ulcers, infective ulcer or wounds that do not heal after amputations or other surgical operation.

There are also some medical prerequisites for application of the apparatus. The causative disorders and conditions must be treated: improvement of venous backflow through surgical sen-

Table 1. Baseline characteristics of patients in both groups (n=17)

	Group	
	Control	Experimental
All	73	66
Gender		
Female	40	36
Male	33	31
Age (yr)	19-86	23-79
Cause of injury		
Trauma	16	17
Compression	15	13
Vasculogenic	14	15
Diabetes	18	16
Infection	10	6

sitization or compression therapy, regulation of blood sugar level, release of pressure from amputation stumps, decubitus wounds etc. Patients should not be allergic to aerosols.

Scheme of application

The trial consisted of a clinical comparison between a group of patients who were treated with routine treatment- "moist" wound treatment: after cleaning the wound surface thoroughly (removal of adherent deposits and crusts) by using saline, Vaseline will be used as a water-impermeable occlusion of the wound and a sterile bandage was applied, and a second group of patients who received negative-charged aerosols in addition of routine treatment. The total number of patients included in the study was 140. The patients were randomly assigned to each of these two groups. The aerosols were applied on daily basis (2 hours per time, twice a day). The end point of the study was the time at which the chronic wounds healed completely.

Culture identification of wound infection

Samples were collected from 140 subjects' chronic wounds at the First Affiliated Hospital of Sun Yat-Sen University (Guangzhou, Guangdong, P. R. China) in accordance with Hospital clinical laboratory techniques protocol. Samples were tested using routine aerobic culture techniques in a hospital certified laboratory in the First Affiliated Hospital of Sun Yat-Sen University. Chronic wound infection was identified and confirmed with culture swab growth of moderate or many colonies. Swab cultures were reported as none or colonies positive.

Digital photograph for healing assessment

Starting on day zero and then at post-treatment day 7, 14, 21 and 28, relative wound size was measured by gravitational planimetry. The wound margins were traced by using transparent film paper (Office Master, Zhonghua, China) cut-out and weighed. Wound area was calculated as a percent of original and remaining wound size: $\left(\frac{remaining}{original}\right)\times 100$. Digital images of the wounds were captured by using a xx digital camera.

Statistical analysis

All quantitative data are presented as mean ± standard error of mean (SEM). Statistical differences of measurement data were determined using Student's t-Test, Statistical differences of enumeration data were compared using χ^2-Test, Difference was considered significant at $P< 0.05$.

Results

140 patients were recruited and fulfilled for the study. All patients completed the study period and no patient was excluded from the study analysis. The demographic profile was comparable in the two groups (**Table 1**, $P>0.05$).

Wound observation

Control group have more necrotic tissue surround or above the wounds compared with experimental group. The surface exudation and swelling condition of this group were severer. Edematous, pale granulation tissue can be observed on control wounds.

Surface exudation and swelling condition of experimental group can be apparently alleviated after the treatment of negative-charged aerosols. The appearance of wounds granulation tissue is clean, healthy and rosy.

Detection of bacteria in wound secretions

Wound secretions were collected at selected time points (post-treatment day 0, 10, 14, 21 and 28) and were used for bacterial culture,

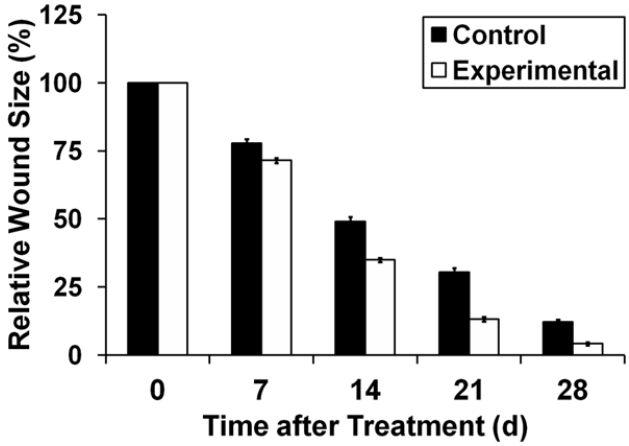

Figure 2. The wound healing process of patients in the experimental and control group. Compared with control group (77.48 ± 1.52%), the relative wound size of experimental group (71.49 ± 0.85%) was significantly smaller after treatment since day 7 (P<0.05). The greatest difference in relative wound size was observed on day 28 where the relative wound size of control group was approximately 2.9 fold as large as experimental group (12.15 ± 0.96% vs. 4.8 ± 0.58% in control and experimental group, respectively, P<0.05).

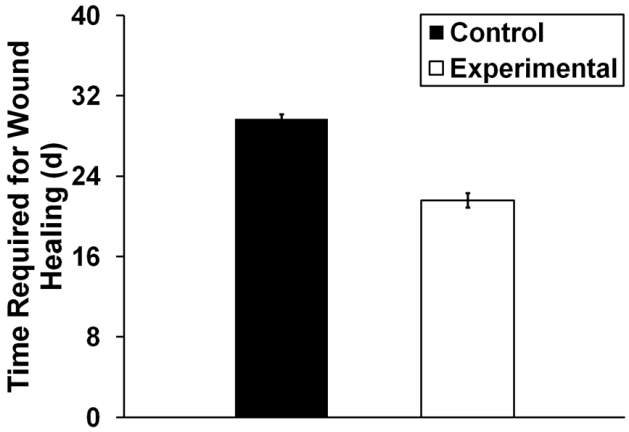

Figure 3. The time required for wound healing in the experimental group (21.60 ± 0.71 d) was significantly shorter than that in the control group (29.70 ± 0.45 d, P<0.05).

bacterial infection in two groups has no significant difference at day 0 (P>0.05). The difference of infection rate between two groups was significant (P<0.05) at all the selected time points (**Figure 1**).

The efficacy of aerosols therapeutic apparatus on wound healing

To investigate the therapeutic efficacy of negative-charged aerosols therapeutic apparatus on the healing of chronic wounds, we observed the wound healing process of patients in the experimental and control group. Compared with control group (77.48 ± 1.52%), the relative wound size (**Figure 2**) of experimental group (71.49 ± 0.85%) was significantly smaller after treatment since day 7 (P<0.05). The greatest difference in relative wound size was observed on day 28 where the relative wound size of control group was approximately 2.9 fold as large as experimental group (12.15 ± 0.96% vs. 4.8 ± 0.58% in control and experimental group, respectively, P<0.05). Additionally, the time required for wound healing (**Figure 3**) in the experimental group (21.60 ± 0.71 d) was significantly shorter than that in the control group (29.70 ± 0.45 d, P<0.05).

Discussion

The wounds failed to proceed through an orderly and timely process to produce anatomic and functional integrity, or proceeded through the repair process without establishing a sustained anatomic and functional result can be defined as chronic wounds [18]. Represent a serious medical and societal problem [19], chronic wounds lead to a substantial reduction in quality of life caused by pain and immobility. Social isolation and financial problems may be further consequences.

Affected by many factors, the pathogenesis of chronic wound is complex, which results in the coexistence of various treatments. But there is no ideal treatment has been recognized so far [20, 21]. The negative-charged aerosols therapeutic apparatus is a special electronic devices which can produce negatively charged aerosol with a particle size of 5 μm. These aerosols can infiltrate into the human body through skin, mucous membranes, respiratory tract and wounds and affect the metabolism process as well as activity of the cells [22]. Various biological effects have been observed in experimental animals and in patients exposed to the negative-charged aerosols, as discussed by Wehner [23, 24], and Krueger [25]. Currently accepted effects of negative-charged aerosols include improved resistance to infection; improved clinical status of patients with respiratory tract diseases. Introducing negative-

charged aerosols into the treatment of skin wounds, studies of Yingbing Xu and Tao Zhan have shown that [10, 26]: these aerosol can effectively promote cyclin C and PCNA expression by up-regulating EGF and β1 integrin expression, and finally promote cell proliferation as well as accelerating wound healing. Additionally, as reported by Yeyang Li, these aerosols can promote wound healing by enhancing the proliferation level of epidermal stem cells [27], which may act as one of the mechanisms promoting chronic wound healing. According to our observation, it was showed that the negative-charged aerosol can effectively reduce surface exudation and swelling condition of wounds. The granulation tissue of the experimental group wounds was in a health status which confirmed the anti-infection effect of the negative-charged aerosol [11, 28, 29]. By analyzing healing rate and time required for chronic wound closure our research also confirmed the promotion effect of negative-charged aerosol.

It is supported by our observation as well as other study that [10], the aerosol do not have adverse effects on patients during treatment, but the application of negative-charged aerosols still have some details worth notice based on the treatment experience we have: (1) avoiding contact with metal objects during treatment; (2) due to the existence of electric potential difference, weak electric shock like feeling may be experienced when touch the patients undergoing therapeutic treatment. But it will not cause any severe damage; (3) therapy shall be effective when instrument be placed within 30 cm apart from the wounds; (4) after every time of use, clean apparatus with 75% ethanol.

Acknowledgements

The project was supported by National Natural Science Foundation of China; Grant # 81071557, supplemental support from the Department of Burns Surgery at First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong, China.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Julin Xie, Department of Burns Surgery, First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong 510080, China. E-mail: gz3x111@163.com

References

[1] Freedman G, Cean C, Duron V, Tarnovskaya A, Brem H. Pathogenesis and treatment of pain in patients with chronic wounds. Surg Technol Int 2003; 11: 168-79.

[2] Franks PJ, Moffatt CJ, Doherty DC, Smithdale R, Martin R. Longer-term changes in quality of life in chronic leg ulceration. Wound Repair Regen 2006; 14: 536-41.

[3] Stuart BO. Deposition of inhaled aerosols. Arch Intern Med 1973; 131: 60-73.

[4] O'Doherty MJ, Miller RF. Aerosols for therapy and diagnosis. Eur J Nucl Med 1993; 20: 1201-13.

[5] Krueger AP, Smith RF. Effects of air ions on isolated rabbit trachea. Proc Soc Exp Biol Med 1957; 96: 807-9.

[6] Krueger AP, Smith RF. Effects of gaseous ions on tracheal ciliary rate. Proc Soc Exp Biol Med 1958; 98: 412-4.

[7] Krueger AP, Smith RF. The effects of air ions of the living mammalian trachea. J Gen Physiol 1958; 42: 69-82.

[8] Krueger AP, Smith RF, Millar JW. Effects of air ions on trachea of primates. Proc Soc Exp Biol Med 1959; 101: 506-7.

[9] Krueger AP, Smith RF. The biological mechanisms of air ion action. II. Negative air ion effects on the concentration and metabolism of 5-hydroxytryptamine in the mammalian respiratory tract. J Gen Physiol 1960; 44: 269-76.

[10] Li TZ, Xu YB, Hu XG, Shen R, Peng XD, Wu WJ, Luo L, Dai XM, Zou YT, Qi SH, Wu LP, Xie JL, Deng XX, Chen E, Zhang HZ. [Clinical study and pathological examination on the treatment of deep partial thickness burn wound with negative charge aerosol]. Zhonghua Shao Shang Za Zhi 2005; 21: 266-9.

[11] Seo KH, Mitchell BW, Holt PS, Gast RK. Bactericidal effects of negative air ions on airborne and surface Salmonella enteritidis from an artificially generated aerosol. J Food Prot 2001; 64: 113-6.

[12] Kerr KG, Beggs CB, Dean SG, Thornton J, Donnelly JK, Todd NJ, Sleigh PA, Qureshi A, Taylor CC. Air ionisation and colonisation/infection with methicillin-resistant Staphylococcus aureus and Acinetobacter species in an intensive care unit. Intensive Care Med 2006; 32: 315-7.

[13] Wehner AP, Craig DK, Stuart BO. An aerosol exposure system for chronic inhalation studies with rodents. Am Ind Hyg Assoc J 1972; 33: 483-7.

[14] Shepherd SJ, Beggs CB, Smith CF, Kerr KG, Noakes CJ, Sleigh PA. Effect of negative air ions on the potential for bacterial contamination of plastic medical equipment. BMC Infect Dis 2010; 10: 92.
[15] Kellogg EW 3rd, Yost MG, Barthakur N, Kreuger AP. Superoxide involvement in the bactericidal effects of negative air ions on Staphylococcus albus. Nature 1979; 281: 400-1.
[16] Siddiqui AR, Bernstein JM. Chronic wound infection: facts and controversies. Clin Dermatol 2010; 28: 519-26.
[17] Atiyeh BS, Dibo SA, Hayek SN. Wound cleansing, topical antiseptics and wound healing. Int Wound J 2009; 6: 420-30.
[18] Lazarus GS, Cooper DM, Knighton DR, Margolis DJ, Pecoraro RE, Rodeheaver G, Robson MC. Definitions and guidelines for assessment of wounds and evaluation of healing. Arch Dermatol 1994; 130: 489-93.
[19] Sen CK, Gordillo GM, Roy S, Kirsner R, Lambert L, Hunt TK, Gottrup F, Gurtner GC, Longaker MT. Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen 2009; 17: 763-71.
[20] Costin GE, Birlea SA, Norris DA. Trends in wound repair: cellular and molecular basis of regenerative therapy using electromagnetic fields. Curr Mol Med 2012; 12: 14-26.
[21] Game FL, Hinchliffe RJ, Apelqvist J, Armstrong DG, Bakker K, Hartemann A, Löndahl M, Price PE, Jeffcoate WJ. A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes. Diabetes Metab Res Rev 2012; 28 Suppl 1: 119-41.
[22] Xu YB, Li TZ, Qi SH, Zhang T, Xie JL, Ke CN, et al. [Influence of aerosol bioelectricity on expression of epidermal growth factor and β1 integrin in healing wounds of burned rats]. Journal of Third Military Medical University (Di-San Junyi Daxue Xuebao) 2005; 27: 1229-1231.
[23] Wehner AP. Negatively charged aerosols. Effect on pulmonary clearance of inhaled 239 PuO 2 in rats. Chest 1971; 60: 468-71.
[24] Wehner AP. Electro-aerosols, air ions and physical medicine. Am J Phys Med 1969; 48: 119-49.
[25] Krueger AP, Reed EJ. Biological impact of small air ions. Science 1976; 193: 1209-13.
[26] Zhang T, Li TZ, Xu YB, Qi SH, Liang HZ, Xie JL, Chen XD, Zheng SS. [Influence of aerosols on the expression of cyclin B1, cyclin C and proliferating cell nuclear antigen in wound tissue healing of burned rat models]. Zhonghua Wai Ke Za Zhi 2005; 43: 1280-3.
[27] Li YY, Li TZ, Xie JL, Qi SH, Xu YB, Bian HN. [Changes of epidermal stem cells in burned wounds of the rats after treatment by the aerosol with negative electric charge]. Chinese Journal of Experimental Surgery 2005; 22: 1447-1449.
[28] Fan L, Song J, Hildebrand PD, Forney CF. Interaction of ozone and negative air ions to control micro-organisms. J Appl Microbiol 2002; 93: 144-8.
[29] Tyagi AK, Nirala BK, Malik A, Singh K. The effect of negative air ion exposure on Escherichia coli and Pseudomonas fluorescens. J Environ Sci Health A Tox Hazard Subst Environ Eng 2008; 43: 694-9.