The Effect of oral N-Acetylcystein on prevention of extensive tissue destruction in electrical burn injury

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The effect of oral N-acetylcystein on prevention of extensive tissue destruction in electrical burn injury

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ABSTRACT

Background: Electric burn patients usually suffer permanent injury and sequelae. Salvage of the zone of stasis is an important topic in the treatment of burn patients. N-Acetylcysteine (NAC), as an antioxidant, has effect on the saving zone of stasis and extensive rhabdomyolisis. The aim of this study was therefore to evaluate the effect of oral NAC on tissue destruction indicators in an electric burn rat model.

Material and methods: An experimental study was conducted with thirty six male Wistar albino rats divided into 2 groups. Group A (n=18) and group B (n=18) were electrical burn injury groups without and with NAC therapy, respectively. The extent of burn wounds were evaluated by planimetry using a digital wound measuring device. Blood samples were obtained to analyze creatine kinase (CK) levels as a marker of extensive rhabdomiolysis on the first hour after electric injury (baseline) and on the 7th day to see the antioxidant effect of NAC.

Results: A significant decrease in tissue destruction was seen by the necrotic area on day 7 in the NAC therapy group compared to the control group (mean 2.26±1.05 cm^2 versus mean 7.12 ±3.30 cm^2 respectively; p=0.001), which was confirmed by the level of serum CK (day 7: group A, mean 140±51 U/L versus Group B, mean 102±6 U/L; p=0.007).

Conclusion: A decrease in electric burn necrotic area and tissue damage in the group using NAC treatment was demonstrated. NAC might have a beneficial effect in the treatment of electrical burns. Further experimental and clinical studies with NAC treatment are necessary to confirm these results.

1. Introduction

Electrical burns occur in 3-5% of thermal burns patients [1,2], and cause serious injury in 1000-1500 people every year around the world with a mortality rate of 20-30%. Permanent injury and sequelae were seen in 74% of patients who survived [3,4].

Electrical burns, especially high-voltage injuries, often cause damage to the skin and deeper structures, resulting in large areas of necrosis. However, the severity of tissue damage depends on several factors, including the intensity of the electrical burn (high vs. low voltage), the current type (direct or indirect), the amount of electrical load, which body part is injured, the contact time, and the difference of resistance [5].

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Severe damage can lead to multi-organ failure (e.g. heart, kidney, nerves, eyes). Furthermore, injury in the extremities often lead to amputation, with the possibility of amputation of the affected fingers in low voltage electrical injuries.

A disturbance in the microvascular circulation is the main reason for severe tissue necrosis in electrical injury. The current treatment is still lacking in terms of prevention of tissue damage and organ damage due to electrical injury. Some studies report that antioxidant therapy is beneficial in overcoming the oxidative stress that develops during the wound healing process, particularly in electrical burns [6]. It has been shown that N-acetylcysteine (NAC) protects tissue damage caused by free radicals [7,8] by an increase in the levels of glutathione. NAC has already been used as a scavenger of oxygen free radicals, with many satisfactory results [6]. With oral antioxidant therapy, NAC is expected to prevent extensive tissue destruction from electrical burns, and thus reduce the morbidity and mortality rate.

2. Material and methods

This is a randomized controlled animal study that is performed in the Airlangga University Medical Faculty Biochemistry Experimental Animal Laboratory between June 2017 and July 2017. The Animal Care and Use Committee (ACUC) Faculty of Veterinary Medicine of Airlangga University Surabaya Indonesia approved this study protocol. The Ethical Clearence number is 756-KE.

2.1. Animals and experimental procedure

Thirty six male Wistar albino rats weighting between 350 and 400 g were divided into 2 main experimental groups. Group A (n=18) and B (n=18) were electrical burn injury groups without and with NAC therapy, respectively. Two separate analyses were performed at different time points on 9 out of 18 rats from Group A and B at each time point. Biochemistry (creatine kinase levels) and necrotic areas at the 1st hour and at day 7 after electrical injury were evaluated. The animals were cared in standard laboratory conditions throughout the study.

2.2. Electrical burn injury

All animals were anesthetized with intramuscular injection of ketamine hydrochloride (50 mg/kg) and xylazine hydrochloride (15 mg/kg). Before applying the electrode, the left upper extremity and right lower extremity of the rats were shaved and ultrasound gel was used as a conductive material above the skin. A phase electrode was placed on the left upper extremity and the neutral electrode was placed on the right lower extremity. The extremities were exposed to 220 V AC for 10 s approximately 450-500 mA current applied.

2.3. N-Acetylcystein (NAC) therapy

Oral N-acetylcystein effervescent tablet (600 mg; Fluimucil, PT. Zambon Indonesia) with a therapeutic dose (600 mg/kg/day) was administered 15 min after electrical burn injury.

Since we used male Wistar albino rats weighting between 350 and 400 g, we dissolved the 600 mg effervescent tablet into 5 mL of water. Then, the solution was administered in concordance with a therapeutic dosage, about 1.5-2cc by an oral gavage 20G needle. The N-acetylcystein was given every day, 15 min after injury, for in total 7 days. The dosage of NAC was determined in accordance with previous reports of therapeutic doses [9].

2.4. Biochemical evaluation

Creatine kinase (CK) can be used as a marker of tissue damage. Measurement of serum CK activity is still an important indicator of muscle cell necrosis and tissue damage due to disease or trauma. Based on the literature, progression of tissue damage can be assessed based on the increase in serum CK [10]. CK level measurements were performed with 3 mL of blood specimen extracted from cardiac puncture. Blood was stored in an EDTA tube at 4-10°C temperature, and processed within 6 h after blood extraction.

2.5. Evaluation of necrotic areas

Necrotic area in this study is the area of skin exposed to electrical burns, causing a necrotic zone [11]. This zone macroscopically appears as a bluish color, gray to black with clearly defined borders. For planometric measurements, we used Visitrak Digital (Smith & Nephew Medical LTD, England). We measured the zone using a template (transparent plastic sheet), and then interpolated in order to obtain Visitrak output broad zones within cm^2. The necrotic areas of the left upper and right lower extremities were measured.

2.6. Statistical analysis

Non-parametric tests were used, such as the Kruskal-Wallis Test, the Wilcoxon Signed Rank Test, and the Mann-Whitney Test, since both variables were not normally distributed.

The Kruskal Wallis Test was used to analyze the difference between all 4 groups (2 groups of necrotic areas and 2 groups of CK levels).

The Mann-Whitney Test was used to analyze the difference between unpaired groups. In this study, it was used to analyze the difference between a CK level control group day 0 and day 7, CK level treatment group day 0 and day 7, CK level control group day 0 and CK level treatment group day 0, CK level control group day 7 and CK level treatment group day 7, necrotic area control group day 0 and necrotic area treatment group day 0, and necrotic area control group day 7 and necrotic area treatment group day 7.

The Wilcoxon Signed Rank Test was used to analyze the difference between two paired groups. In this study, it was used to analyze the difference between necrotic area control group day 0 and day 7, and between necrotic area treatment group day 0 and day 7. This test was also used to analyze the difference between CK level control group day 0 and day 7, and between CK level treatment group day 0 and day 7.

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3. Results

Nine mice from Group A at day 7 suffered significant more tissue necrosis with some compartment syndrome on their extremities (mean necrotic area 7.12±3.30cm^2; Figs. 1 and 2) compared to nine mice from Group B (mean necrotic area 2.26 ±1.05cm^2; p=0.007).

This significant difference of tissue necrosis between Group A and B at day 7 was also confirmed by the level of serum CK. Mean baseline value of serum CK at day 0 (1st hour) for Group A was 5244±4350U/L and Group B was 10898 ±6674U/L (Fig. 3). At day 7, Group A had a mean value of serum CK of 140±51U/L in comparison to 102±6U/L in Group B (p=0.007; Fig. 4).

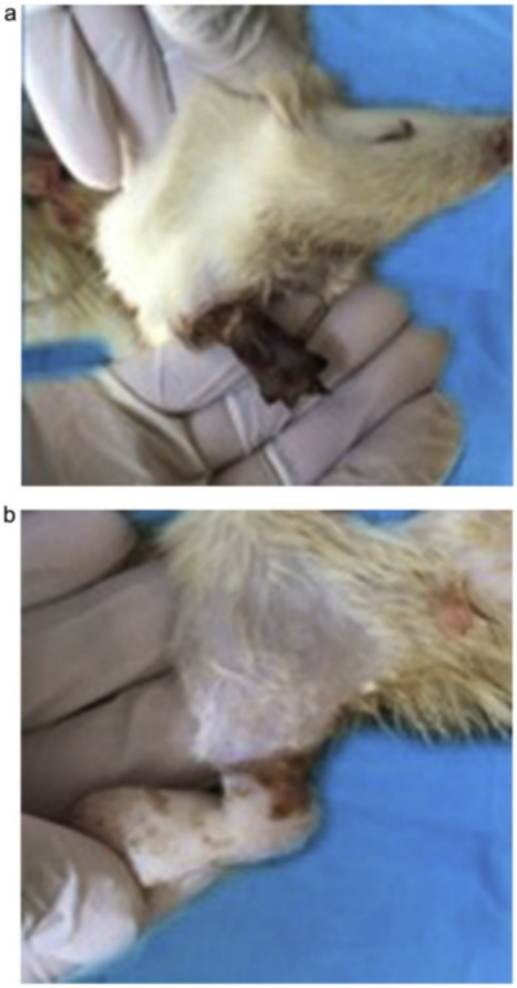

Fig. 1 – Clinical comparison of extremities between Group A and B at day 7.
(A) A significant severe necrotic area on the right front foot of a Group A mouse at day 7 (notice the compartement syndrome that it suffered resulting more devastating tissue necrosis).
(B) Small necrotic area on the left hind foot of a Group B mouse at day 7 (notice the burn injury was also circumferential without any signs of compartment syndrome).

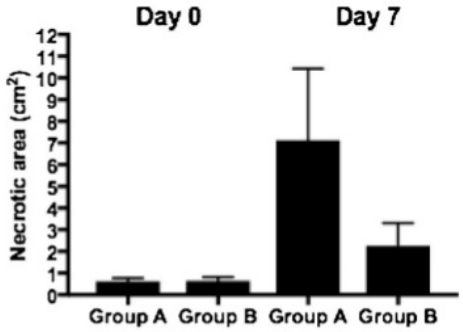

Fig. 2 – Mean necrotic area (cm^2) at day 0 and day 7 in group A compared to group B.

4. Discussion

The effects of NAC have already been evaluated in several clinical studies, demonstrating that it has been used as a treatment modality for multiple diseases, such as cancer, cardiovascular diseases, diabetes [12], human immunodeficiency virus infections, liver and respiratory diseases [13–15]. In these diseases, oxidative stress is generated, which is defined by an imbalance between reactive oxygen species (ROS) and antioxidants. Also, in severe (electrical) burn patients, ROS and Reactive Nitrogen Species (RNS) are elevated in burned tissue. It has been shown that antioxidant therapy is beneficial in combating oxidative stress.

Sahib et al. showed that several antioxidants, including NAC, were useful in the treatment of patients with a burn injury, because it results in less wound infections and complications [16]. NAC, as an antioxidant, is a scavenger of free radicals as it interacts with ROS [17]. However, there are no reports comparing electric burn necrotic area and CK levels in severe electrical burns with or without NAC treatment. The beneficial effect of NAC in burn injury is confirmed by our study, in which a significant decrease in electric burn necrotic

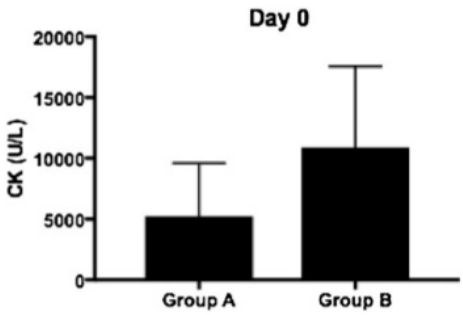

Fig. 3 – Mean value of serum CK at day 0 in group A compared to group B.

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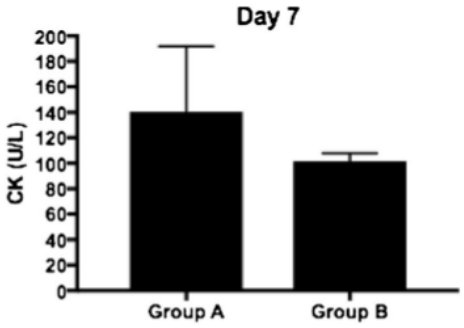

Fig. 4 – Mean value of serum CK at day 7 in group A compared to group B.

area and tissue damage was seen in the group using NAC in an electric burn rat model. At the end of the 7th day, we found that the area of necrosis was prevented clearly by NAC in group B.

Furthermore, multiple animal studies were performed investigating the effect of NAC in burn wouds. One of these studies of Deniz et al. showed that NAC prevented tissue necrosis by saving the zone of stasis in a rat comb-burn model. They compared a group where NAC was administered orally or intraperitoneally with a control group, and evaluated the extent of burn wound and malondialdehyde levels. This study concluded that rats receiving NAC had a lower burn wound width. No significant differences were seen in malondialdehyde concentrations [18]. Another study of Tsai et al. also reported promising results regarding the use of NAC in a burn wound healing rat model. Better re-epithelialization was seen in wounds of rats treated with 3.0% NAC topically, and thus wound healing might be accelerated [19].

Csontos et al. analyzed the effect of NAC in a patient population (n=30). One group (n=15) received standard therapy, whereas in the other group (n=15) NAC was supplemented. Several mediators of oxidative stress and inflammation were measured. They showed that treatment with NAC resulted in a significant increase in glutathion on days 4-5, and significant lower inflammatory mediators, such as IL-6, IL-8, and IL-10. Thus, NAC leads to less oxidative stress and inflammation [20].

NAC is a precursor in glutathion formation. In burn injury, ROS is produced and several inflammatory cells cause tissue damage and finally multiple organ failure. Glutathione is elevated by NAC, and however, prevents cell damage caused by ROS.

NO-mediated vasodilation can be increased by NAC [18], thereby reducing the incidence of obstruction, ischemic thrombosis and ultimately necrosis of muscle tissue, which is confirmed in our experimental study showing decreased serum CK levels in Group B at day 7. Besides that, NAC has multiple advantages, such as easy applicable in oral form, effective, low costs, and safe.

In conclusion, in this experimental study, a significant decrease in electric burn necrotic area and CK levels was shown in the group using NAC treatment. Therefore, NAC might have a beneficial effect in the treatment of electrical burn injury. Further experimental and clinical studies with NAC treatment are necessary to confirm these results.

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Conflict of interest statement

There are no editorial or financial conflicts of interest.

REFERENCES

[1] Mirmohammadi SJ, Mehrparvar Amir Houshang, Kazemeini K, Mostaghaci Mehrdad. Epidemiologic characteristics of occupational burns in Yazd, Iran. Int J Prev Med 2013;4(6):723-7.
[2] Kumar S, Ali W, Verma AK, Pandey A, Rathore S. Epidemiology and mortality of burns in the Lucknow Region, India—a 5 year study. Burns 2013;39(8):1599-605.
[3] Esses SI, Peters WJ. Electrical burns; pathophysiology and complications. Can J Surg 1981;24(1):11-4.
[4] Xiao J, Cai BR. A clinical study of electrical injuries. Burns 1994;20(4):340-6.
[5] Bailey S. Electrical injuries. Considerations for the perioperative nurse. AORN J 198949(3) 773-6, 8-81, 84-87.
[6] Turkmen Suha M. Effects of N-acetylcysteine and ethyl pyruvate on ischemia-reperfusion injury in experimental electrical burn model. Am J Emerg Med 2016;34(7):1217-24.
[7] Jeremias A, Soodini G, Gelfand E, Xu Y, Stanton RC, Horton ES, et al. Effects of N-acetyl-cysteine on endothelial function and inflammation in patients with type 2 diabetes mellitus. Heart Int 2009;4:e7.
[8] Katherine A, Lyseng-Williamson CMP. Micronised purified flavonoid fraction a review of its use in chronic venous insufficiency, venous ulcers and haemorrhoids. Drugs 2003;63 (1):71-100.
[9] Saleh AAS. Synergistic effect of N-acetylcysteine and folic acid against aspartame-induced nephrotoxicity in rats. Int J Adv Res 2014;2(5):363-73.
[10] Kopp Jürgen, Loos B, Spilker Gerald, Horch Raymund E. Correlation between serum creatinine kinase levels and extent of muscle damage in electrical burns. Burns 2004;30:680-3.
[11] Jackson DM. The diagnosis of The Depth of Burning. Br J Surg 1953;40(164):588-96.
[12] Atkuri KR, Mantovani JJ, Herzenberg LA. N-Acetylcysteine—a safe antidote for cysteine/glutathione deficiency. Curr Opin Pharmacol 2007;7:355-9.
[13] Kelly GS. Clinical applications of N-acetylcysteine. Altern Med Rev 1998;3:114-27.
[14] Anonymous. N-Acetylcysteine. Altern Med Rev 2000;5:467-71.
[15] Zafarullah M, Li WQ, Sylvester J, Ahmad M. Molecular mechanisms of N-acetylcysteine actions. Cell Mol Life Sci 2003;60(Jan 1):6-20.
[16] Sahib AS, Al-Jawad FH, Alkaisy AA. Effect of antioxidants on the incidence of wound infection in burn patients. Ann Burns Fire Disasters 2010;23:199-205.
[17] Zafarullah MLW, Sylvester J, Ahmad M. Molecular mechanisms of N-acetylcysteine actions. Cell Mol Life Sci 2003;60:6-20.

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[18] Deniz M, Borman H, Seyhan T, Haberal M. An effective antioxidant drug on prevention of the necrosis of zone of stasis: N-acetylcysteine. Burns 2013;39(March (2)):320–5.
[19] Tsai ML, Huang HP, Hsu JD, Lai YR, Hsiao YP, Lu FJ, et al. Topical N-acetylcysteine accelerates wound healing in vitro and in vivo via the PKC/Stat3pathway. Int J Mol Sci 2014;15(May (5)):7563–78.
[20] Csontos C, Rezman B, Foldi V, Bogar L, Drenkovics L, Röth E, et al. Effect of N-acetylcysteine treatment on oxidative stress and inflammation after severe burn. Burns 2012;38(May (3)):428–37.

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