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Therapeutic Effectiveness of *N*-Acetyl Cysteine for Burn-Related Acute Renal Failure

Hamid Noshad, Ahmad Abasgholizadeh, Arezou Hamzehzadeh Alamdari, Morteza Ghojazadeh

Department of Internal Medicine, Kidney Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

ABSTRACT

Objective: This study aimed to evaluate the effects of *N*-acetyl cysteine administration on burn patients complicated with acute renal failure.

Methods: In this prospective, randomized, double-blind, placebo-controlled clinical trial, 69 patients with burn injury were studied. Eligible subjects were patients with burn injury, complicated with acute renal failure within 5 days post-burn. In the study group, 600 mg of *N*-acetyl cysteine was supplemented every 8 hours orally, while the control group was given the placebo. Serum levels of urea and creatinine and urine volume were closely monitored.

Results: Sixty-two participants (32 men and 30 women; age range 19-56 and mean ± SD, 35.66 ± 9.68) completed the trial. The mean serum urea and creatinine levels, estimated glomerular filtration rate, and urine volume were improved in both patient groups, without any significant difference between the groups (analysis of covariance, $P > .05$). The mean length of stay in the hospital for all subjects was 10.14 ± 1.67 days which was 11.22 ± 1.33 days in the control group and 9.06 ± 1.23 days in the study group. Data show a significant decrease in the duration of hospitalization in the patients who were receiving *N*-acetyl cysteine compared to those who were receiving the placebo ($P = .001$).

Conclusion: There were no significant differences in primary endpoints between subjects treated with *N*-acetyl cysteine or placebo, and the potential therapeutic effectiveness of *N*-acetyl cysteine for burn-related acute renal failure failed in this study. However, the study results are in favor of the *N*-acetyl cysteine treatment due to the significantly reduced length of in-hospital stay.

Keywords: N-acetyl cysteine, acute renal failure, burn, urea, creatinine, eGFR

Corresponding author: Arezou Hamzehzadeh Alamdari ✉ arezou.hamzehzadeh@gmail.com

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INTRODUCTION

Multiple biological actions of *N*-acetyl cysteine (NAC), the acetylated form of amino acid cysteine, are widely acknowledged. In particular, acting as a precursor for L-cysteine in the synthesis of hepatic glutathione and regenerating glutathione stores as its antioxidant effect has been evidenced.[1,2] *N*-acetyl cysteine has been widely used in the prevention of hepatic injury as an acetaminophen antidote and for the dissolution of thick mucosa as a mucolytic.[3] Beyond that, the protective effects of NAC on the kidney have been indicated. Although its accurate effect on renal cells remains unclear, its protective effects are likely connected to the decrease in oxidative stress. In chronic renal failure (CRF), it slows down disease progression, and in acute renal failure (ARF), it attenuates the injury that was caused by contrast, ischemia, nephrotoxins, surgery, and obstruction. Furthermore, reported significant decreases in serum creatinine levels after NAC administration in healthy individuals emphasizes the importance of NAC effects on the kidney.[4,5]

Burn-induced acute renal failure (ARF) is a potential serious complication that afflicts 10%-30% of burn patients and is associated with 73%-100% attributive mortality, which is much higher than the mortality rate in uncomplicated burn.[6,7] Based upon the timing of its onset, it can be divided into early-onset or late-onset ARF. In the framework of early-onset disease, it occurs within 5 days post-burn and is mainly caused by increased vascular permeability that leads to fluid shift, hypovolemia, and eventually cardiac output reduction. Myoglobinuria can trigger ARF as an early complication as well. On the other hand, late-onset ARF arises after day 5 and is predominantly initiated by sepsis.[7,8] Destruction of the physical skin barrier is the main cause of susceptibility to infections in burn patients. However, the initial response of the immune system to severe injuries and inflammatory cascade activation plays an important role in sepsis susceptibility and developing systemic inflammatory response syndrome and multiple organ dysfunctions in burn patients as well.[9-11]

Various experimental and clinical studies have investigated NAC effects on attenuating organ injury.[12,13] Effects of NAC to prevent the development of ARF following many different causes have yielded conflicting results.[14,15] More studies are required to determine prophylactic and therapeutic effects of NAC on acute kidney damage. This study aimed to evaluate the effects of NAC administration on burn patients complicated with ARF. The therapeutic effectiveness of NAC on serum urea and creatinine levels and urine volume on these patients was the main outcome of interest. An additional outcome studied was the length of in-hospital stay.

METHODS

This study was approved by the Ethics Committee of the Tabriz University of Medical Sciences (Approval Date: November 11, 2019; Approval Number: IR.TBZMED.REC.1398.846), and written informed consent was obtained from all the participants or nearest relatives.

This prospective, single-institution, randomized, double-blind, placebo-controlled clinical trial, in which 69 patients with burn injury were studied, was carried out in the kidney research center, from September to December 2019.

Eligible subjects were patients with burn injury, caused by any thermal energy, greater than 20% total body surface area involvement, who were admitted to the hospital in the first 24 hours of the injury with normal renal function at the admission. Among the eligible subjects, patients complicated with ARF within 5 days post-burn as per the definition of the Kidney Disease Improving Global Outcomes (KDIGO) guideline were enrolled in the study. Acute renal failure and its diagnostic criteria according to the KDIGO 2012 ARF guidelines are defined as follows: increase in serum creatinine $\geq$ 0.3 mg/dL within 48 hours or increase in serum creatinine $\geq$1.5 times the baseline within 7 days or decrease in urine volume $<$ 0.5 mL/kg/h for 6 hours.[16]

Subjects who were younger than 18 years or with a past medical history of any chronic kidney disease and CRF or subjects who were unwilling or unable to provide informed consent were excluded.

Burn percentage and degree were recorded for each patient. Blood samples were collected in the admission and repeated every 24 hours, and serum urea and creatinine levels were recorded. Urine output was monitored hourly.

Next, participants were randomly assigned to the study group or control group using a computer-generated randomization list in a double-blind fashion. In the study group, 600 mg of NAC was supplemented every 8 hours orally, while the control group was given the placebo. Serum levels of urea and creatinine and urine volume were closely monitored. The trial was called complete for each case when the serum creatinine level remained stable for 72 consecutive hours.

Sixty-nine subjects were enrolled in this study and 62 of them were included in the final analysis. Seven cases were excluded due to in-hospital death.

Statistical Analysis

The statistical analysis of this study was conducted using SPSS software Version 18 (SPSS Inc, Chicago, USA). All categorical variables were reported as frequency and percentage, and numerical variables were reported as mean $\pm$ standard deviation (SD). Based upon the variable to be studied, parametric and non-parametric tests were applied for data analysis. Paired *t*-test and analysis of covariance (ANCOVA) were used. P values less than .05 were considered statistically significant.

RESULTS

Among the included cases (32 men and 30 women; age range 19-56 and mean $\pm$ SD, 35.66 $\pm$ 9.68), 31 (15 men and 16 women; age mean $\pm$ SD, 35.22 $\pm$ 9.48) were in the study group and 31 (17 men and 14 women; age mean $\pm$ SD, 36.09 $\pm$ 10.02) in the control group. There were no significant differences between the groups regarding age, sex, burn surface area, and initial laboratory results. Demographic, initial, and final laboratory data for both groups are summarized in Table 1.

MAIN POINTS

- The potential therapeutic effectiveness of NAC for burn-related AFR was failed in this study.
- NAC administration reduced the duration of hospitalization for burn-related AFR patients.
- The study results are in favor of the NAC treatment due to the significant reduced length of in-hospital stay.

Table 1. Patients' Demographic and Laboratory Data in the Beginning and at the End of the Trial

	Study Group (N = 31)	Control Group (N = 31)	*P*
Age (years)	35.22 ± 9.48	36.09 ± 10.02	.726
Male/female	15/16	17/14	.611
Burn surface area (%)	30.48 ± 4.15	30.64 ± 6.92	.912
Initial serum creatinine (mg/dL)	2.79 ± 0.69	2.86 ± 0.67	.711
Final serum creatinine (mg/dL)	1.04 ± 0.11	1.05 ± 0.11	.913
Initial eGFR, (mL/min/1.73 m^2)	25.59 ± 7.34	25.48 ± 8.01	.958
Final eGFR, (mL/min/1.73 m^2)	76.05 ± 16.58	76.36 ± 13.73	.936
Initial serum urea (mg/dL)	54.58 ± 10.17	54.80 ± 9.54	.929
Final serum urea (mg/dL)	23.06 ± 3.35	22.22 ± 3.34	.328
Initial urine volume (mL/h)	38.93 ± 11.38	41.83 ± 9.88	.288
Final urine volume (mL/h)	55.74 ± 6.08	50.77 ± 7.74	.007
Duration of hospitalization (days)	9.06 ± 1.23	11.22 ± 1.33	.001

Except for sex (number of patients) other data are mean ± standard deviation.
eGFR, estimated glomerular filtration rate.

The mean serum creatinine level was decreased markedly in both patient groups (from 2.86 ± 0.67 mg/dL to 1.05 ± 0.11 mg/dL in the control group and from 2.79 ± 0.69 mg/dL to 1.04 ± 0.11 mg/dL in the study group) without any significant difference between the groups (ANCOVA, P = .760). Likewise, the estimated glomerular filtration rate (eGFR) that was calculated for each patient using the creatinine-based formula shows an increase from 25.48 ± 8.01 to 76.36 ± 13.73 in the control group and from 25.59 ± 7.34 to 76.05 ± 16.58 in the study group with no significant difference between the groups (ANCOVA, *P* = .937).

Serum urea was decreased from 54.80 ± 9.54 mg/dL to 22.22 ± 3.34 mg/dL and from 54.58 ± 10.17 mg/dL to 23.06 ± 3.35 mg/dL in the control and the study group, respectively, whereas there was no significant association between NAC administration and decrease in the serum urea levels (ANCOVA, *P* = .654).

Urine output elevation was noticed from 41.83 ± 9.88 mL/h to 50.77 ± 7.74 mL/h in the control group and from 38.93 ± 11.38 mL/h to 55.74 ± 6.08 mL/h in the study group. The increased volume of urine was not significant comparing the 2 groups (ANCOVA, *P* = .071).

The mean length of stay in the hospital for all subjects was 10.14 ± 1.67 days which was 11.22 ± 1.33 days in the control group and 9.06 ± 1.23 days in the study group. Data show a significant decrease in the duration of hospitalization in the patients who were receiving NAC compared to those who were receiving placebo (*P* = .001).

DISCUSSION

This study suggested no therapeutic effectiveness for NAC in burn-related ARF in the adult population. Serum urea and creatinine and urine output volume showed no significant difference between the patients who were receiving NAC and those receiving placebo. However, the length of stay in the hospital was reduced significantly by NAC administration. To the best of our knowledge, this is the first study assessing the therapeutic effectiveness of NAC on burn-induced ARF. However, multiple studies have investigated the prophylactic effects of NAC on ARF associated with the other causes[17-19] or have evaluated the beneficial effects of NAC in burn patients.[10,20,21]

There were no significant differences in primary endpoints between subjects treated with NAC or placebo, and the potential therapeutic effectiveness of NAC for burn-related AFR failed in this study. Therapeutic benefits as well as its prophylactic effects of NAC administration are vague.[22] Many researches have yielded conflicting results regarding NAC's beneficial effects on preventing ARF. *N*-acetyl cysteine for the prevention of ARF related to contrast, prolonged hypotension, perioperative cardiovascular, and elective aortic aneurism repair failed in separate studies.[14,18,23] However, an animal study has evidenced beneficial effects of prophylactic NAC on cisplatin-induced ARF by the negative regulatory effect of p38 mitogen-activated protein kinase activation as an oxidation-associated signal, through inhibition of oxidative stress.[15] Another animal study, conducted on rats subjected to renal ischemia–reperfusion, evidenced kidney function improvement with NAC administration.[24] Furthermore, a meta-analysis concluded NAC is beneficial for the prevention of contrast-induced nephropathy in patients with pre-existing CRF.[25]

In this study, NAC administration resulted in shortening of in-hospital stay and was consistent with several other studies that have shown beneficial effects of NAC administration in a burn injury. The edema in burn patients is generated following oxidative stress and inflammation which can be eliminated by NAC administration.[10] Oxidative damage is responsible for pathophysiological events in burn injury, not only in the local tissue but also in the other organs. In other words, early treatment with antioxidants can eliminate burn-related injuries remarkably.[20] Moreover, research has shown antioxidants in burn injury can restrict wound infection, shorten the healing time, and reduce the mortality rate.[21]

CONCLUSION

There were no significant differences in primary endpoints between subjects treated with NAC or placebo, and the potential therapeutic effectiveness of NAC for burn-related AFR failed in this study. However, the study results are in favor

of the NAC treatment due to the significant reduced length of in-hospital stay.

Ethics Committee Approval: Ethics committee approval for this study was obtained from the Ethics Committee of the Tabriz University of Medical Sciences (Approval Date: November 11, 2019; Approval Number: IR.TBZMED.REC.1398.846).

Informed Consent: Written informed consent was obtained from the participants or nearest relatives.

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Declaration of Interests: The authors have no conflict of interest to declare.

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