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Assessment of Add-On Therapy of N-Acetylcysteine in the Management of Acute Pancreatitis

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Abstract

Background Acute pancreatitis (AP) is an inflammation of the pancreas. The conservative therapeutic options include enteral nutrition, antibiotics, and/or surgery. Oxidative stress in AP has been pathologically linked with the systemic inflammatory response. N-acetylcysteine (NAC), an antioxidant, attenuates oxidative stress-induced cell injury and other potential pathological events in AP.

Objective This article evaluates the treatment outcome of NAC combined with conventional therapy in AP patients and assesses the difference in the duration of hospital stay between the NAC with conventional therapy group and the conventional therapy group.

Materials and Methods This observational study was conducted in a tertiary care hospital with 65 AP patients above 18 years of age. The effect of adding NAC with conventional therapy (intravenous hydration 0.9% normal saline, pancreatin, optional antibiotics) was assessed in patients by comparing serum amylase, lipase, Acute Physiology and Chronic Health Examination (APACHE) II score, and Ranson's score, before and after therapy and the difference in duration of hospital stay was assessed using the independent *t*-test.

Results Of the 65 AP patients, 62% ($n = 40$) were on conventional therapy and 38% ($n = 25$) were on NAC along with conventional therapy. The difference in mean values of reduced serum amylase between the two treatment groups indicates a significant difference ($p = 0.01$). However, the variance in mean serum lipase values was statistically insignificant ($p = 0.1$). The mean scores of Ranson's criteria showed no significant difference between both groups ($p = 0.4$). There was a significant difference in APACHE II severity scores after 24 ($p = 0.04$) and 48 hours ($p = 0.01$), respectively. Similarly, the mean duration of hospital stay in both treatment groups was found to be statistically insignificant ($p = 0.4$).

Conclusion Both treatment options, conventional therapy and NAC combined with conventional therapy, resulted similar treatment outcomes for AP patients, with no additional benefits observed.

Keywords
- amylase
- APACHE II
- lipase
- N-acetylcysteine
- pancreatitis
- Ranson's criteria

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Introduction

Acute pancreatitis (AP) is a common clinical condition ranging from mild self-limiting disease to severe necrotizing pancreatitis with high mortality. The global incidence of AP has increased over time, with an average annual percentage change from the 1960s to 2016 being 3.07%, and the number of incident cases was 2.8 million. The incidence has been varying considerably worldwide, with an increased incidence among the elderly.[1,2] The most commonly diagnosed types of AP include idiopathic, alcohol-related, and gallstone/bile-related.[3] Unlike severe pancreatitis, early AP does not manifest organ failure and pancreatic necrosis but if persistent for >48 hours can increase severity. Therefore, precise prediction of the disease requires early addressing and severity detection.[4] Initial evaluation of AP is performed by assessing serum lipase or amylase levels, along with liver biochemistry. Severity assessments have been done using different tools and scoring systems such as Ranson's criteria, revised Atlanta criteria for severity, BISAP (Bedside Index of Severity in AP), and APACHE II (Acute Physiology and Chronic Health Examination II), where the latter is said to be more accurate in predicting the outcome of the disease after 48 hours, in at least 88% of the cases.[3] Guidelines for managing AP include fluid resuscitation using Ringer's lactate, normal saline, and other intravenous fluids along with analgesics and antiemetics, as the initial treatment.[5] Antibiotics have been recommended for infected pancreatitis. Other interventional surgeries include endoscopy, cholecystectomy, etc., depending on the severity and etiology of AP.[6] The pathophysiology of AP involves enzymatic activation in pancreatic acinar cells, leading to inflammation and infiltration of proinflammatory factors and leukocytes into the gland. This subsequently causes oxidative stress and cell damage. NAC works by preventing the increase in cytosolic Ca^{2+} concentration and reduce the accumulation of enzymes in acinar cells during AP. It is an antioxidant capable of restoring the levels of glutathione, the most important cellular antioxidant. It also prevents oxidative free radicals' production and therefore attenuates oxidative cell damage. A meta-analysis of antioxidant treatment for AP reported a reduction in patient complications.[7] Since the therapeutic effect of NAC in the management of AP has been underexplored, this study observes the treatment outcome of NAC along with conventional therapy which is intravenous hydration—0.9% normal saline, pancreatin, and optional antibiotics.

Materials and Methods

This was a prospective observational study performed in the department of gastroenterology of a tertiary care hospital for a duration of 1 year from June 2020 to May 2021. The study was approved by the Institutional Human Ethical Committee. A count of 65 AP patients above 18 years of age was taken in to study. Patients with chronic pancreatitis, pregnant population, and pediatric population were excluded from the study. Written informed consent was obtained from all the patients. Demographic data, serum levels of amylase and lipase, and duration of hospital stay were collected. Patients were classified into two groups, those who received conventional therapy (0.9% normal saline, pancreatin, and optional antibiotics) and NAC with conventional therapy (NAC infusion: 1 g/5 mL + 25 mL normal saline followed by oral tablet of 600 mg twice a day). The effect of NAC with conventional therapy over conventional therapy was assessed in AP patients by comparing serum amylase (normal range: 40–140 U/L) and serum lipase (normal range: 10–140 U/L). Also, severity and mortality assessment were assessed using APACHE II score and Ranson's score, before and after therapy. APACHE II score, which proves to be the best in predicting the severity of the disease and prognosis, consists of 14 parameters and is used here in analyzing mortality score in the treatment groups. Ranson's score, a standard predictor of outcome in AP patients, is unique in assessing 11 parameters and is also used in the study for disease severity and mortality assessment. Both the scores are opted for their difference in their parameters assessed and for their specificity and sensitivity.

Either minimization or prolongation in duration of hospital stay was assessed in both treatment groups. The significance of outcomes in the management of AP with NAC as an add-on was assessed by an independent *t*-test for the *p*-value of 0.05 and confidence interval at 95%, by using SPSS version 26 as a statistical tool.

Results

Of the total population, the majority of the patient were male (93%, $n=60$) followed by female (7%, $n=5$). A maximum number of patients were in the age group of 40 to 49 (27.6%). Among the participants 54% were diagnosed as an idiopathic AP, 25% were alcohol-related, and 15.50% were gallstone-induced (biliary pancreatitis). A count of 40 (62%) were receiving conventional therapy and 25 (38%) were receiving NAC along with conventional therapy.

Assessment of Biochemical Parameters

The mean values of serum amylase and serum lipase were calculated at two different time points; one at baseline, at the time of initiation of treatment for AP, and other after 24 hours of treatment. The mean values of serum amylase observed at baseline of patients were 292 U/L in conventional therapy and 225 U/L in NAC with conventional therapy. These mean values were decreased to 163 and 144 U/L, respectively, after 24 hours of treatment in both groups. The serum amylase values were greatly reduced in conventional therapy (129 U/L) compared with NAC with conventional therapy (81 U/L). The difference in mean values of reduced serum amylase between these two groups showed that there is a significant difference in both the treatment groups ($p=0.01$).

The baseline mean serum lipase values were observed to be 266 U/L in conventional therapy and 230 U/L in NAC with conventional therapy. It was found to be decreased in both treatment groups as 167 and 179 U/L, respectively. From the

Table 1 Assessment of biochemical parameters

Biochemical parameters	Time points	Conventional therapy (mean)	NAC with conventional therapy (mean)	*p*-Value
Amylase	At admission	292	225	0.1
	After therapy	163	144	0.1
	Mean difference	129	81	**0.01**[a]
Lipase	At admission	266	230	0.2
	After therapy	167	179	0.2
	Mean difference	99	65	0.1

Abbreviation: NAC, N-acetylcysteine.
[a]Indicates significance at $p < 0.05$.

difference between the mean serum lipase values obtained, it was found that serum lipase values were decreased at a greater level in conventional therapy (99 U/L) compared with NAC with conventional therapy (65 U/L) and was found to be statistically insignificant ($p = 0.1$). Clinically, both amylase and lipase values reduced in a similar way in both the groups which showed almost identical outcome. This is mentioned in ►**Table 1**.

Assessment of Severity Scores

Ranson's score was analyzed by obtaining the mean mortality rate values at the time of admission and it was 0.6 in both conventional therapy and NAC with conventional therapy. After 24 hours of treatment, the mean score values were 0.4 in conventional therapy and 0.5 in NAC with conventional therapy which shows 0.2 and 0.1 difference between the mean scores in both treatment groups, respectively. This result did not show any significant difference ($p = 0.4$). The mortality score based on Ranson's criteria is approximately similar in both treatment groups, the addition of NAC with conventional therapy does not show any changes in the score.

The mean value of APACHE II severity score was 2 at the time of admission in both treatment groups. After 24 hours it was found to be 1.2 in conventional therapy and 1.8 in NAC with conventional therapy, and after 48 hours it was 0.8 in conventional therapy and 1.6 in NAC with conventional therapy. There was a significant difference in this severity score between the groups after 24 ($p = 0.04$) and 48 hours ($p = 0.01$), respectively. The severity score was greatly reduced in conventional therapy after 24 and 48 hours. This is mentioned in ►**Table 2**.

Assessment of Duration of Hospital Stay

The mean duration of hospital stay in the conventional therapy (5.9 ± 2) was more or less similar, when compared with the NAC+ conventional therapy (6.0 ± 4) and was found to be statistically insignificant ($p = 0.4$). This reveal adding NAC with conventional therapy neither prolongs nor shortens the duration of hospital stay.

Assessment of Etiological Factors

Besides overall outcome of the treatment in all AP patients the effect of NAC was also specifically assessed on the idiopathic and alcohol-induced AP patients using the same abovementioned parameters, to check, does the varied etiological factors in the development of AP has any relation in the outcome of treatment by adding NAC with conventional therapy. In idiopathic AP patients, the APACHE II scores for both conventional and NAC with conventional therapy had showed a similar outcome following to the 24 ($p = 0.04$) and 48 hours (0.001) of the treatment. This is mentioned in ►**Table 3**. Similarly, in alcohol-induced AP patients, it was found that the APACHE II scores, serum amylase, and serum lipase values at admission and after therapy had no

Table 2 Severity assessment of patients using Ranson's criteria and APACHE II

Severity parameters	Time points	Conventional therapy (mean)	NAC with conventional therapy (mean)	*p*-Value
Ranson's criteria	At admission	0.6	0.6	0.5
	After therapy	0.4	0.5	0.2
	Mean difference	0.2	0.1	0.4
APACHE II	At admission	2	2	0.3
	After 24 hours of therapy	1.2	1.8	**0.04**[a]
	After 48 hours of therapy	0.8	1.6	**0.01**[a]
	Mean difference	1.2	0.4	0.1

Abbreviations: APACHE II, Acute Physiology and Chronic Health Examination II; NAC, N-acetylcysteine.
[a]Indicates significance at $p < 0.05$.

Table 3 Treatment outcomes among idiopathic acute pancreatitis patients

Parameters	Time points	Conventional therapy	NAC with conventional therapy	*p*-Value
Amylase (U/L)	At admission	292	226	0.1
	After therapy	163	144	0.1
Lipase (U/L)	At admission	266	230	0.2
	After therapy	166	179	0.2
Ranson's	At admission	0.6	0.6	0.5
	After 24 hours	0.4	0.5	0.2
APACHE II	At admission	2.3	2	0.3
	After 24 hours	1.2	2	**0.04**[a]
	After 48 hours	1	2	**0.007**[a]
Duration of hospital stay (mean ± SD, d)		7 ± 12	6 ± 7	0.2

Abbreviations: APACHE II, Acute Physiology and Chronic Health Examination II; NAC, N-acetylcysteine.
[a]Indicates significance at $p < 0.05$.

significant difference in the outcome of NAC with conventional therapy compared with conventional therapy. It is evident that the etiological factor does not show any remarkable changes in influencing the treatment outcome. This is mentioned in ►**Table 4**.

Discussion

A randomized, double-blind, placebo-controlled trial by Siriwardena et al,[8] revealed that there was no difference in APACHE II scores between active and placebo therapy during the first 7 days of treatment, indicating no variance in mortality rates. Similarly, the assessment of mortality rates in AP patients with APACHE II scores showed comparable outcomes after 24 and 48 hours of treatment with conventional therapy as well as NAC combined with conventional therapy.

In addition to the APACHE II score, we also evaluated serum amylase, serum lipase, and Ranson's criteria at admission and after 24 hours of treatment, revealing no significant differences between the two treatment groups. Furthermore, we separately examined the impact of NAC on patients with idiopathic and alcohol-induced AP. Our findings indicate that NAC combined with conventional therapy did not exhibit any significant effects compared with conventional therapy alone in our study. However, there is a lack of human studies supporting these findings, underscoring the necessity for further similar investigations to substantiate the effectiveness of NAC as an adjunct to conventional therapy in AP patients.

A study conducted by Sateesh et al[9] demonstrated reduced oxidative stress and an enhanced antioxidant status in AP patients when clinically assessed. Antioxidant supplementation may potentially reduce hospital stay duration and complication rates in AP patients, but further validation through larger clinical trials is necessary to confirm this hypothesis. However, in our study, the duration of hospital stays did not exhibit any significant differences. It is noteworthy that most of the referenced studies are clinical trials, while our observational study also has a smaller sample size, indicating the need for a larger sample size to strengthen our

Table 4 Treatment outcomes among alcohol-induced acute pancreatitis patients

Parameters	Time points	Conventional therapy	NAC with conventional therapy	*p*-Value
Amylase	At admission	360	126	**0.01**[a]
	After therapy	176	114	**0.01**[a]
Lipase	At admission	283	178	**0.04**[a]
	After therapy	178	158	0.3
Ranson's	At admission	0.9	0.6	0.3
	After 24 hours	0.4	0.4	0.3
APACHE II	At admission	2.2	2	0.8
	After 24 hours	1	2	0.1
	After 48 hours	0.6	2	0.05[a]
Duration of hospital stay (mean ± SD, d)		6 ± 10	7 ± 5	0.4

Abbreviations: APACHE II, Acute Physiology and Chronic Health Examination II; NAC, N-acetylcysteine.
[a]Indicates significance at $p < 0.05$.

findings and provide sufficient evidence to support our hypothesis.

Limitations

Our study has limited sample size, thereby posing challenges in assessing the efficacy of NAC when administered along with conventional therapy. Specifically, within the idiopathic and alcoholic subgroups, this combined treatment regimen showed no statistically significant outcomes compared with conventional therapy alone, attributable in part to the restricted number of participants ($n = 25$) who received NAC alongside conventional therapy. A more expansive sample size and an interventional study are imperative to support the hypothesis of this study. However, the absence of recent research that supports our hypothesis complicates the acquisition of relevant scholarly works.

Conclusion

In this study, both treatment options, conventional therapy and NAC with conventional therapy, demonstrated similar treatment outcomes for AP patients. This indicates that adding NAC to conventional therapy does not provide any additional benefits in treating AP. Additionally, in both idiopathic and alcohol-induced AP patients, NAC with conventional therapy showed treatment outcomes similar to conventional therapy alone. This suggests that the underlying cause of AP does not significantly influence treatment outcomes. Considering the potential benefits of NAC as an effective antioxidant supplement, we recommend conducting further studies with larger populations to confirm this hypothesis.

Declaration

The study was performed in accordance with the Declaration of Helsinki.

Informed Consent

Obtained from all the study participants.

Ethical Approval

The study obtained Human Ethics permission from the Institutional Human Ethical Committee. The approval date and number are March 29, 2019, and IHEC # 106, respectively.

Conflict of Interest

None declared.

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