

Original Research Article

The beneficial role of N-acetylcysteine as an adjunctive drug in treatment of COVID-19 patients in a tertiary care hospital in India: an observational study

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ABSTRACT

Background: N-acetyl cysteine, a mucolytic agent, demonstrates free radical scavenging and anti-inflammatory properties, and prevents endothelial dysfunction by inhibition of NF-KB and formation of no adducts. This has a potential role to tackle cytokine storms, endothelial dysfunction and prothrombotic state observed in COVID-19 manifestations like ARDS and Multi organ dysfunction.

Methods: Institution based descriptive cross sectional study, 164 patients from laboratory confirmed RT PCR positive COVID-19 patients, in the study period from 27th May 2020 to 10th August 2020, were assessed, in medical college Kolkata, a dedicated COVID-19 care facility.

Results: It was observed that moderate-severe patients who received N-acetyl cysteine along with standard therapy had average hospital stay duration of 12 days, higher rate of discharge, average duration of oxygen therapy of 8 days, less number of deaths and reduced transfer to critical care facilities.

Conclusions: N-acetyl cysteine can be considered as an adjunctive therapy with standard protocol driven care, due to its beneficial anti-inflammatory and free radical scavenging properties.

Keywords: COVID-19, N-acetyl cysteine, Free radical scavenger, Anti-inflammatory

INTRODUCTION

A new severe acute respiratory syndrome caused by the novel coronavirus (SARS-CoV-2), has started an outbreak in Wuhan, in the province of Hubei in China from December 2019 and then has rapidly caused a pandemic around the World.¹ It has caused multi organ dysfunction, some of which are ARDS, pneumonia with pulmonary haemorrhage and hepatic, cardiac and renal injury and also prothrombotic state varying from pulmonary embolism, myocardial infarction, DIC, stroke and death.²

Though the exact mechanism is still a matter of discussion, primarily it has affected the respiratory system although other system involvement like CNS, is also present.³

It has been shown in a study of Carsana et al, that all the COVID-19 cases under study had features of exudative and proliferative changes in the alveoli ranging from capillary congestion, hyaline membrane and pneumocyte destruction and necrosis, intra alveolar and interstitial oedema and thrombus plug formation.⁴ Apart from this patients have increased concentrations of

proinflammatory cytokines like IL6, IL1, TNF alpha which give rise to cytokine storm in the body.⁵ Reactive oxygen species (ROS) and free radicals are produced in the body and wide spread free radicals induced injury is seen.

Thus any drug with a good antioxidant property and a free radical scavenging property can be really promising as a supportive treatment. Although specific treatment towards COVID-19 virus is still under study, many adjuncts or supportive treatment strategies have been postulated, one such promising repurposed drug is N-acetyl cysteine (NAC). This can considerably reduce the progression of patients to severe disease forms and reduce in hospital mortality and post-discharge comorbidity.

Objectives of study

The objectives of the study was to assess the demographic profile of COVID-19 patients admitted in a tertiary hospital of Eastern India, with focus on comorbidities and COVID-19 disease category and to understand the role of N acetyl cysteine as an adjunctive treatment option alongside standard protocol driven care, and its effect on COVID-19 patients in terms of outcome (number of deaths, transfer to ICU facility and duration of hospital stay, number of discharges).

There is lack of data regarding the beneficial role of N-acetyl cysteine in COVID-19 patients. This study attempts to fill the gap in knowledge, as it explores the beneficial role of N-acetylcysteine across different severity categories of COVID-19 patients, in a tertiary care hospital of Eastern India.

Review of literature

N-acetyl cysteine is a thiol compound and a mucolytic agent. It is a precursor of L-cysteine and reduced glutathione.⁶ It is converted to cysteine by acylase 1 and cysteine with glutamine forms gamma glutamyl cysteine by glutamine cysteine ligase, this is the rate limiting step in the formation of glutathione. Gamma glutamyl cysteine with glycine forms glutathione by glutathione synthetase. This is the reduced form of glutathione which acts as the free radical scavenger. Ratio of reduced glutathione to oxidized glutathione measures the oxidative stress in the body and the major amount is in the reduced form.⁷ This is the indirect antioxidant property of NAC. It also exerts direct antioxidant property by scavenging specific types of oxidant species like HO(X) (hypohalous acid) and NO₂.^{7,8}

It breaks the di-sulfide bonds in high molecular weight glycoproteins present in the mucus which reduces the viscosity of the mucus. Mucus increases airway resistance and work of breathing, something that is

deleterious for COVID-19 patients, especially with ARDS.

NAC has been shown to inhibit NF-KB expression (nuclear factor kappa B) which acts via EGFR (endothelial growth factor receptor) expression and this influences MUC5AC (gel forming mucins).⁷ Mucus accumulation can decrease the airflow causing obstruction, atelectasis, secondary lung infections and also lung infarction.⁹ Thus NAC acts as an antioxidant and reduces airway inflammation.¹⁰ In both in vivo and human trials NAC, N acetyl cysteine has been seen to decrease pulmonary fibrosis and ARDS.^{11,12} Also it has been studied that it modifies the half life of NO by forming NO adducts, thus it exerts a positive role in improving endothelial function.¹³

A study done by Andrews et al, showed N-acetyl cysteine potentiates acetylcholine mediated dilation of vessels, thus improving endothelial function.¹⁴

In another study by Nishikawa et al, IV infusion has shown significant dilation of vessels in epicardial arteries and increased coronary blood flow.¹⁵

Many clinical trials have been conducted on the role of NAC, in respiratory illness like attenuation of influenza like symptomatology and improvement of cell mediated immunity with long term NAC by De Flora et al where the mucolytic property of the drug has been highlighted and the treatment in the study has been observed to be well tolerated and it has decreased the frequency of influenza like episodes.¹⁶

Another study where the drug has been observed to decrease the symptoms and exacerbations of COPD, and decreased the accelerated lung function decline is, respiratory syncytial virus inhibits cilia genesis in differentiated normal human bronchial epithelial cells, effectiveness of N-acetyl cysteine by Mata et al.¹⁷

Improvement by N-acetyl cysteine of acute respiratory distress syndrome through increasing intracellular glutathione, and extracellular thiol molecules and antioxidant power: evidence of underlying toxicological mechanisms, a study by Soltan- Sharifi et al, this study demonstrated a beneficial role in the deficient oxidant antioxidant balance in ARDS patients by increasing the extracellular oxidant power and thiol molecules and ultimately intracellular glutathione levels.¹⁸

It has been studied that higher concentration in plasma may be achieved after IV administration.¹⁹ Thus injectable form of N-acetyl cysteine, was given to the patients admitted with moderate to severe symptoms and mild category patients received tablet forms, categories done as stated by MOHFW (ministry of health and family welfare).²⁰

METHODS

Study design and patient selection

Hospital based cross sectional study design was performed. The study was conducted in the COVID-19 wards of medical college Kolkata (a designated COVID-19 facility), among patients admitted from 27 May 2020 to 10 August 2020 who gave written informed consent for the study, and having a laboratory confirmed report by RT-PCR method. They were assessed on a daily basis for the outcome with the oral/injectable NAC, and other standard treatment protocol as per clinical guidelines laid down by the ministry of health and family welfare, Government of India.²⁰

Patient selection, procedure, and treatment

The patients were RT PCR lab confirmed COVID-19 patients, ranging from 18 years to 90 years, and included both males and females. They had different comorbidities like hypertension, diabetes, IHD (ischemic heart disorder), COPD (chronic obstructive lung disorder), hypo/hyperthyroidism, pre existing liver or kidney disease, different types of cancer. All the relevant patient's history was taken and noted, and previous medications were also noted. Regularly clinical vitals were checked like, level of consciousness, blood pressure, pulse rate, saturation in room air or on HFNO (high flow nasal oxygen), NRBM (non rebreather mask), whether febrile or afebrile and were documented in a centralised database.

Based on the clinical parameters they were divided into mild, moderate, and severe categories as laid down by the prevalent guidelines of the Government of India at the time of admission in the COVID-19 ward.

According to the category, for mild patients tablet NAC, N-acetyl cysteine (600 mg), one tablet twice daily was given. For moderate to severe patients injection NAC, N-acetyl cysteine (1 gm) IV TDS was given, along with the standard treatment protocol as per India clinical guidelines by ministry of health and family welfare Government of India, and it was given till the patient had a saturation of 99-100% in room air.²⁰ Data collection was analysed and relevant tables/ charts were prepared using Microsoft Excel.

RESULTS

164 patients were included in the study; all of them had confirmed COVID-19 infection tested by RTPCR method. All of them were given the N-acetyl cysteine either in injectable or tablet form and no notable adverse reactions were noted.

Median age of the patients was 62 years (range 20 to 100 years). 114 Males and 50 females were in the study and 67.68% of the patients had one or more comorbidities,

that is, 111 patients out of 164 patients had one or more comorbidities.

Table 1: Age distribution of patients in this study.

Age groups (in years)	Frequency
20-30	1
30-40	9
40-50	21
50-60	65
60-70	40
70-80	15
80-90	11
90-100	2

53 patients out of 164 had diabetes (32%), 81 patients out of 164 had hypertension (49%) and 35 patients had diabetes and hypertension i.e. 57.4% whereas 49 patients out of 164 (30%) had other comorbidities in the form of IHD, liver disease, COPD, or kidney disease, cancer. So the majority of the patients in this study had hypertension and diabetes as comorbidites.

Number of patients found in the mild category was 112, in the moderate category 15 patients and 37 were assigned severe category, thus in the percentage form, 68.29% were in mild category, 9.14% in moderate, and 22.5% in severe category as per MOHFW guidelines.²⁰

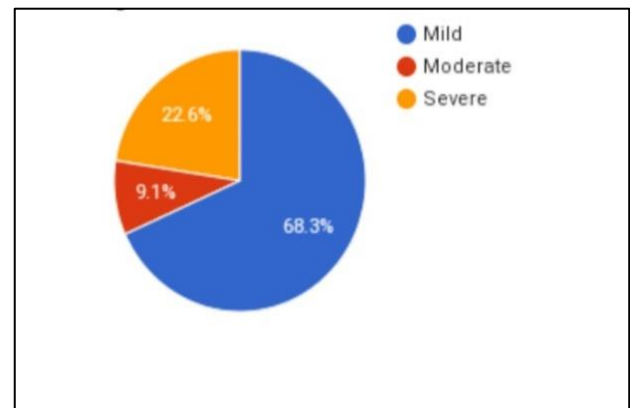


Figure 1: The percentage of mild, moderate, and severely affected patients.

None of these patients were lost to follow up. In terms of outcome, patients received standard care, according to the national guidelines by the MOHFW, along with N-acetyl cysteine. We observed that the moderate to severe category patients were having shorter duration of hospital stay, an average of 12±1.5 days.

In the severe category there was only 1 death out of 37 severe patients and 6 patients from severe category were transferred to CCU, where they received standard care, however these 6 patients did not undergo mechanical ventilation. No death was recorded in other categories. Most moderate-severe category patients undergoing

treatment in the General COVID-19 wards (15 moderate category + 31 severe category patients), were on oxygen therapy for an average duration of 8 days since time of admission.

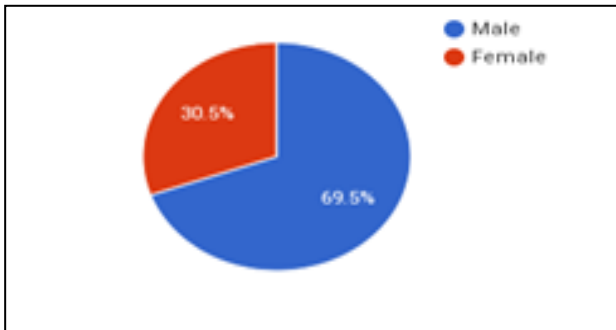


Figure 2: Distribution of males and females in the study.

From moderate category only 2 patients out of 15 patients were transferred to CCU and none of them needed mechanical ventilation. Overall the patients in the study had 97% discharge rate, and death occurred in 1.82%, and 4.8% were transferred to CCU facility. The case fatality rate of this medical college was observed to be 1.82% which is much less than the average National rates for the study period.²¹ No adverse effects due to the drug were reported.

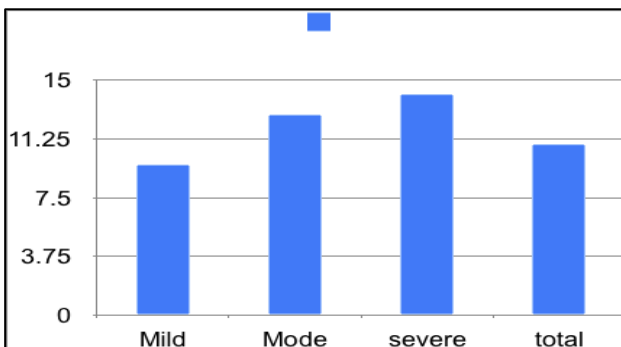


Figure 3: Average duration of hospital stay (days) in different category patients.

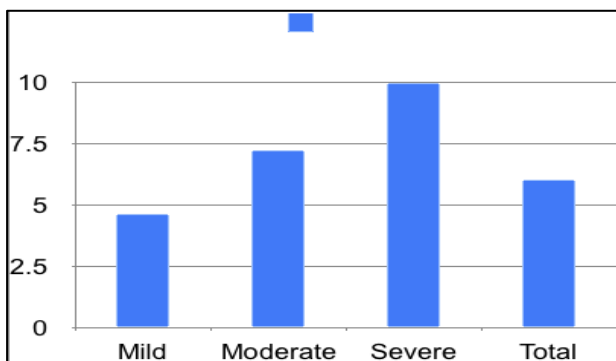


Figure 4: Average duration of oxygen therapy (days) in different category of patients.

DISCUSSION

As of now no proven treatment for COVID-19 has been formulated. We have been aiming towards symptomatic management so as to reduce the complications of the disease and the duration of stay in hospital, and to look for a better outcome in terms of more discharges, and lesser transition towards mechanical ventilation/ECMO (extra corporeal membrane oxygenation) support.

Along with the treatment provided in national guidelines, the addition of this drug, N-acetyl cysteine has shown tremendous positive results in the outcome by decreasing the duration of stay, lesser number of deaths, more discharges. On an average prior to using NAC as adjunct drug, the mean number of days of hospital stay was 16 days, as noted from in-hospital records of this institution for patients belonging to moderate-severe category with multiple comorbidities. Our observation noted that the average length of stay was reduced to 12 ± 1.5 days. A higher number of patients also required oxygen support for a longer duration >12 days on an average prior to use of NAC whereas we noted an average duration of 8 days, among moderate-severe patients. This effect can mainly be attributed to the mucolytic activity, direct and indirect antioxidant properties and free radical scavenging property and regulation of endothelial function by NAC. The reduction in length of hospital stay and duration on oxygen support is highly beneficial in terms of socio-economic aspects as it reduces the stress on tertiary health facilities, at the same time, by improving the patient parameters, by reducing the dependency of patients on oxygen support, reduced transfer to critical care facilities it is also having potential health benefits.

Similar studies on N acetyl cysteine like N-acetyl cysteine as a potential treatment for COVID-19 by Rangel Mendez et al has shown positive results in the COVID-19 patients and explored the potential of the drug to help flatten the exponential contagion curve.²²

Limitations of study

This is an observational study, limited by sample size, lack of precedence of similar studies in a tertiary hospital in India. Multi centric, randomised control trials are required. Moreover, only clinical criteria and duration of hospital stay was assessed in this study. Biochemical parameters were not assessed. Various confounding factors may have influenced the study results. Drug synergism effect with other components of standardised protocol driven care cannot be ruled out and therapeutic dose monitoring was not performed in patients.

CONCLUSION

N acetyl cysteine can be considered as an adjunctive therapy with standard protocol driven care, due to its beneficial anti-inflammatory and free radical scavenging properties. It has a potential role in reduction of duration

of hospital stay, dependency on oxygen therapy, reduced mortality and transfer to critical care facilities.

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