The Effect of N-Acetyl Cysteine Therapy in the Management of Infections on Patients with Chronic Kidney Disease

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**ABSTRACT**

Chronic Kidney Disease (CKD) is a very common longstanding disease of the kidney leading to renal failure. More than 10 million cases per year in India are reported. People with kidney disease can be more prone to infection because of related conditions such as uremia, diabetes, inadequate calorie and protein intake, and the access site can be vulnerable to infection. Individuals on dialysis therapy have a high risk for infection. N-acetyl cysteine (NAC) is a slightly modified version of sulphur-containing amino acid cysteine. NAC is used as prophylactic therapy for infections. When taken internally, NAC replenishes intracellular levels of the natural antioxidant glutathione (GSH); helping to restore cells ability to fight damage from reactive oxygen species (ROS). NAC has been used successfully to treat glutathione deficiency in a wide range of infections, genetic defects and metabolic disorders. The aim of the study is to determine the effect of NAC on prevention of infection, by measuring C-Reactive Protein (CRP), in patients with CKD. In this study, we also analyze the effect of NAC in retarding the progression of CKD.
INTRODUCTION

Chronic kidney disease (CKD) also called chronic renal insufficiency (CRI) is defined as a progressive loss of kidney function occurring over several months to years and is characterized by the gradual replacement of normal kidney architecture with interstitial fibrosis\(^1\).

The symptoms of worsening kidney function are not specific and might include feeling generally unwell and experiencing a reduced appetite. Often, CKD is diagnosed as a result of screening of people known to be at risk of kidney problems, such as those with high blood pressure or diabetes and those with a bloodline relative with CKD. This disease may also be identified when it leads to one of its recognized complications, such as cardiovascular disease, anemia, pericarditis or renal osteodystrophy.

CKD is identified by a blood test for creatinine, which is a breakdown product of muscle metabolism. Higher levels of creatinine indicate a lower glomerular filtration rate and as a result a decreased capability of the kidneys to excrete waste products. It is a reciprocal relationship, the higher the creatinine, the lower the glomerular filtration rate (GFR). All individuals with a GFR <60 ml/min/1.73 m\(^2\) for 3 months are classified as having CKD\(^1\).

Creatinine levels may be normal in the early stages of CKD, and the condition is discovered if urinalysis (testing of a urine sample) shows the kidney is allowing the loss of protein or red blood cells into the urine. To fully investigate the underlying cause of kidney damage, various forms of medical imaging, blood tests, and sometimes a kidney biopsy (removing a small sample of kidney tissue) are employed to find out if a reversible cause for the kidney malfunction is present. The most common recognized cause of CKD is diabetes mellitus.

The CKD population is predisposed to adverse infectious events because of overwhelming uremia, which is associated with alterations in primary host defense mechanisms and increases the risk of bacterial infections\(^2\).

Neutrophils exhibit impaired chemotaxis, oxidative metabolism, phagocytic activity, degranulation, intracellular killing and dysregulated programmed cell death. Factors contributing to neutrophil dysfunction include malnutrition, trace element deficiencies, iron overload, impaired glucose metabolism, hyperparathyroidism, dialysis and uremic retention solutes.\(^2\)
N-acetyl cysteine (NAC), the acetylated variant of the amino acid L-cysteine. NAC is an excellent source of sulfhydryl (SH) groups and is converted in the body into metabolites capable of stimulating glutathione (GSH) synthesis, promoting detoxification, and acting directly as free radical scavengers. Administration of NAC has historically been as a mucolytic agent in a variety of respiratory illnesses. NAC is a powerful antioxidant and potential therapeutic agent in the treatment of cancer, heart disease, HIV infection, heavy metal toxicity, and other diseases characterized by oxidative damage[^3].

In NAC, which is an acetyl group is attached to the nitrogen atom in cysteine. NAC is then a precursor in the formation glutathione, which is a powerful antioxidant in the body. The sulfhydryl group gives glutathione its antioxidant effect as it is able to reduce free radicals by donating electrons to bond with any unpaired electrons found in the body. Unpaired electrons are usually produced by the body in response to damage, illness and stress. Glutathione is stable even when it donates these electrons; hence it is an excellent antioxidant[^3].

NAC supplementation supported by scientific evidence include prevention of chronic obstructive pulmonary disease exacerbation, prevention of contrast induced kidney damage during imaging procedures, attenuation of illness from influenza when started before infection, treatment of pulmonary fibrosis. NAC is a safe and well-tolerated antioxidant with a well-defined mechanism of action[^4].

The aim of the study is to determine the effect of NAC therapy in the management of infections in patients with chronic kidney disease.

Objectives include:

1. To analyze the effect of NAC on infections by measuring biochemical (C-reactive protein) and hematological parameters.

2. To analyze the effect of NAC in GFR of a chronic kidney disease patients.

3. To evaluate the role of NAC in retarding progression of chronic kidney disease.

**REVIEW OF LITERATURE**

1. Tiemei Zhao *et al.* (2010) conducted a study on “N-acetyl cysteine inhibit biofilms produced by *Pseudomonas aeruginosa*”. Objective of the study was to investigate the inhibitory effects of NAC on biofilms produced by *P. aeruginosa*. The study investigated the
effects of NAC for anti-bacterial properties, detachment of biofilms, viable cells in biofilms. NAC is considered a non-antibiotic drug that has anti-bacterial properties. Twenty *P. aeruginosa* strains were isolated from respiratory samples. The minimum inhibitory concentration (MIC) of NAC for 18 *P. aeruginosa* isolates were 10 to 40 mg/ml, and MIC for another 2 isolates was >40 mg/ml. In conclusion, the result suggests that NAC has anti-bacterial properties against *P. aeruginosa* and may detach *P. aeruginosa* biofilms.[5]

2. Mirja-Liisa Aitio et al. (2005) conducted a study on “N-acetyl cysteine-passe-partout or much ado about nothing?” Studies have reported that administration of NAC (600mg twice daily) in wintertime attenuated influenza and influenza-like episodes, particularly in elderly high-risk persons. Both a systematic quantitative review and a meta-analysis of the existing double-blind placebo-controlled studies on NAC in the treatment of chronic bronchitis arrived at the same conclusion: a prolonged course (3-6 months) of oral NAC with doses from 600mg three times weekly to 400-1200mg daily reduced acute exacerbations and improved symptoms without increasing the risk of adverse effects.[6]

3. Dekhuijzen P.N.R. et al. (2004) conducted a study on “Antioxidant properties of NAC: their relevance in relation to chronic obstructive pulmonary disease”. In an open cross-sectional study performed in 22 smokers with no chronic bronchitis, 19 smokers with chronic bronchitis, with or without airway obstruction, and 14 healthy non-smokers, the bacterial flora and effect of NAC on bacterial numbers were investigated. The number of bacterial colonies was highest in smokers with chronic bronchitis. In addition, the number of intra bronchial bacteria was significantly lower in patients treated with NAC compared to other patients. This effect was more obvious in patients with chronic obstructive bronchitis. The effects of NAC on influenza and influenza-like episodes have been studied in 262 patients suffering from non-respiratory chronic degenerative diseases. Compared to placebo, NAC, 600 mg twice daily for 6 months, resulted in a significant decrease in both the frequency and severity of influenza-like episodes. Local and systemic symptoms were also significantly reduced in the group receiving NAC.[7]

4. Riise G.C et al. (2000) conducted a study on “Inhibitory effect of NAC on adherence of *streptococcus pneumoniae* and *Haemophilus influenzae* to human oropharyngeal epithelial cells *in vitro*”. Objective of the study was to investigate whether NAC influences bacterial adherence as a possible mechanism behind its clinical effects. Highly adhering test strains of *Streptococcus pneumoniae* and *Haemophilus influenzae* were used to investigate the
influence of four pharmacological compounds on adherence to oropharyngeal epithelial cells in vitro. Adhesion assays were performed both during short-term exposure to, as well as long-term incubation with NAC, lidocaine, hydrocortisone and terbutaline at concentrations not inhibiting bacterial growth\[^{[11]}\]. Only NAC showed a significant inhibitory effect on adhesion of *H. influenzae* during short term incubation. NAC lowers bacterial adhesion in vitro to oropharyngeal epithelial cells in doses equivalent to that is being used clinically\[^{[7]}\].

5. **S. De Flora et al. (1997)** conducted a study on “Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term NAC treatment.” A total of 262 subjects of both sexes (78% ≥65 yrs., and 62% suffering from non-respiratory chronic degenerative diseases) were enrolled in a randomized, double blind trial involving 20 Italian Centres\[^{[8, 9]}\]. They were randomized to receive either placebo or NAC tablets (600 mg) twice daily for 6 months. Patients suffering from chronic respiratory diseases were not eligible, to avoid possible confounding by an effect of NAC on respiratory symptoms. NAC treatment was well tolerated and resulted in a significant decrease in the frequency of influenza-like episodes, severity, and length of time confined to bed. Both local and systemic symptoms were sharply and significantly reduced in the NAC group\[^{[10]}\].

**CONCLUSION**

NAC has greater importance in medical practice. NAC has anti-bacterial properties. In infections, NAC treatment decreased the number of bacteria. Patients with NAC had a dose dependent decrease in the rate of rehospitalization. NAC has been used as prophylaxis for infections in patients with chronic kidney disease.

**REFERENCES**