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STUDY OF THE EFFECT OF INHALATIONAL BUDESONIDE ALONG WITH NACETYL CYTEINE ON OXYGEN SATURATION IN COVID 19 SUSPECTED PNEUMONIA PATIENTS

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ABSTRACT

Several studies has been conducted concerning the efficacy of corticosteroids in COVID-19, with evidence to support its use.Moreover there are other evidences which criticize its use .More recently, systemic corticosteroids, in the form of dexamethasone, have been shown to reduce mortality in patients with severe COVID-19. Investigation of gene expression of ACE2 and TMPRSS2 in the sputum of patients with asthma has shown reduced expression of these receptors in the presence of ICS and attenuation of ACE2 receptors in human and murine in-vitro and in-vivo models.12 These findings are highly relevant because SARS-CoV-2 pathology involves TMPRSS2 for spike-protein priming and direct action on the ACE2 receptor, which is highly expressed on epithelial cells in oral mucosa and type 2 alveolar cells. Since evidence exists of accelerated hyperinflammation at the onset of SARS-CoV-2 infection, this hyperinflammation is potentially modifiable by anti-inflammatory treatment. These data suggest a plausible mechanism for efficacy of ICS against COVID-19. We would propose that ICS could have a dual role: first, reducing the inflammatory ARDS-like response affecting a minority of patients with COVID-19; and secondly, directly inhibiting viral replication.Hence a retrospective analysis was done on the suspected covid patients having pneumonia of more than CORAD scale 4.Along with the recommended therapy based on standard guidelines of ICMR 20 patients were given inhalational budecort .After statistical analysis pertaining to improvements in oxygen saturation it was found steroid inhalation improved with due course of time.Alsovarious studies suggests that NAC inhibited oxidative stress and reduced the inflammatory factors in pneumonia. Treatment with antioxidants NAC might reduce oxidative and inflammatory damage in pneumonia patients.Hence a retrospective study was conducted to know the efficacy of inhalational budesonide and N acetyl cysteine on patents having bilateral pneumonia suspected secondary to covid 19 infection.It was observed that oxygen saturation improved with the above mentioned combination .This prevented the need of invasive mechanical ventilation and improves the overall clinical outcome of the patients

KEYWORDS :

INTRODUCTION:

The current COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) infection, raises important questions as to whether pre-morbid use or continuedadministration of inhaled corticosteroids (ICS) affects the outcomes of acute respiratory infectionsdue to coronavirus. During the outburst of the Severe acute respiratory syndrome (SARS) virus in 2003, the role of steroid therapy in the management of acute respiratory illnesses has been debated. The pathogenesis of SARS involves the release of pro-inflammatory cytokines by immune cells called macrophages in the lung alveoli.Steroids inhibit the adhesion and action of cytokines and it has been hypothesised that through such moderation of the immune response, inhaled corticosteroids could prevent the development of acute respiratory distress syndrome.There is an extensive literature to assimilate the current scientific data on this topic.(1)Various stelwarts in the subject had screened approximately 3000 FDA-approved drugs from a drug library against SARS-CoV to identify antiviral drug candidates for therapeutic development(2)Furthermor cytokine storm was a big challenge in covid 19 infection. It was shown that infection with a respiratory virus induced significant down regulation of the antioxidant system in the airway in vivo, and this was likely to result in lung oxidative damage.[3]

Oxidative stress plays an important role in a host's innate immune response to foreign pathogens, and increases the production of inflammation mediators in the respiratory system.[4]Use of N acetyl cysteine was shown to reduce the oxidative stress. Addition of NAC therapy to the patients of pneumonitis reduced MDA(malondialdehyde) and TNF-α and increase TAOC(total antioxidant capacity) more than standard therapy alone..[5].Hence inorder to achieve antiinflamatory response ,replication of viruses and membrane stabilizing effect inhalational budenoside was incorporated in treatment protocol also for reduction of oxidative stress n thereby lung injury ,N acetyl cysteine was used in patients suffering from pneumonitis secondarily to suspected covid 19.

Inclusion Crtiera

Patient ≥ 18 years old and ≤ 75 years old

HRCT depicting suspected COVID-19 infection with CORAD score of more than 4

Hospitalization is required according to current local recommendations

Patient affiliated to a social security regime

Exclusion Criteria:

Oxygen saturation below 85% and above 90% onadmission.

Current treatment with any other inhaled steroid)
Patient with cognitive impairment which do not guarantee proper use of the treatment by the patient himself

Pregnant or breastfeeding women

Participation in another interventional drug study involving human participants and concerning COVID-19 infection or being in the exclusion period of a previous study involving human participants

Contraindications to the treatments (history of hypersensitivity)

Patient admitted for isolation, for social reason or due to comorbidities without gravity sign

Long-term patient treated with digitalis, disopyramide, procainamide or phenothiazine that could lengthen the QT

space.

MATERIAL AND METHODS:

A retrospective analysis is conducted on 40 patients .Group A comprising of control group and group B is of study group where budesonide was administered in the form of nebulization three times a day and inj N acetyl cysteine was administered intravenously 600 mg 12 hrly. Other treatment modality was similar in both the groups.

OBSERVATION AND RESULTS:

Demographic Data

Variables	GROUP A Mean +_SD	GROUP B
Age(yrs)	40.8+_9.80	40.11+_12
Weight(kg)	58.06+_6.88	57.53+_7.7
BMI(kg/m2)	23.83+_6.75	24.66+_6.01

P value >0.05.Demographic data is statistically insignificant

Spo2 in both the groups:

Spo2	Group A	Group B	P value
On admission	86.54+_5.33	85.43+_5.83	> 0.05
Day 2	89.21+_7.17	90.86+_8.60	>0.05
Day 5	90.18+_7.44	94.51+_5.14	<0.05

DISCUSSION:

Explicit discussion has been conducted concerning the efficacy of systemic corticosteroids in COVID-19, with evidence to support its use.Moreover there are other evidences which criticize its use ICS could be a therapeutic intervention for COVID-19 for several reasons. First, inhalational corticosteroid use in patients at risk of acute respiratory distress syndrome (ARDS) has been shown to improve physiology and reduce levels of inflammatory markers.(6) A 50% reduction in ARDS was seen in at-risk patients who were using it before admission to hospital, even after controlling for age, sex, and chronic respiratory diseases.(7) Moreover, use of inhalational corticosteroid also appears to improve pulmonary physiology.(8)

Second, in-vitro data suggest a role for ICS in the inhibition of coronavirus replication (including SARS-CoV-2) in infected epithelial thishyperinflammation is potentially modifiable by anti-inflammatory treatment. These data suggest a plausible mechanism for efficacy of ICS against COVID-19. We would propose that ICS could have a dual role: first, reducing the inflammatory ARDS-like response affecting a minority of patients with COVID-19; and second, directly inhibiting viral replication.

Surprisingly, the prevalence of chronic respiratory disease among patients with SARS and COVID-19appears to be lower than among the general population (9). This is not the case for other chronicdiseases and leads us to hypothesis that lung disease, patients' behaviour or, more likely, theirtreatment may have some protectiveeffective.Sadly,patients with underlying lung disease -19 and are hospitalised have worse outcomes, with a case fatality rate of 6.3%compared to 2.3% overall in China (10). These individuals may have less reserve to cope with thepulmonary effects of severe infection or their immunopathological abnormalities may make them more susceptible to developing pulmonary inflammation and ARDS.

ICS, alone or in combination with bronchodilators, are used extensively in the treatment of asthma(11), and combined with bronchodilators have a role in the management of some patients with COPD(12). There are a number of paradoxes about their effects on viral infections and exacerbation rateswhich are relevant when considering ICS use durig the COVID-19 pandemic. ICS use in asthma andCOPD is associated with an increased risk of upper respiratory tract infections (13, 14).

In peoplewith COPD, ICS use is associated with a higher prevalence of pneumonia (15), and a change in thelung microbiome, although not a change in respiratory virus detection (16). The evidence in asthmais less clear cut, but at least one observational study has shown an increased risk of pneumonia orlower respiratory infection (17). In vitro studies have antiviral innate immune responses (18, 19) and that ICS use leads to delayed virus clearance (20).Other studies, however, have shown normal responses in patients on ICS (21). It is important tonote that most studies have been carried out with rhinovirus and there may be differences in theresponse to other viruses.Conversely, there is evidence to suggest that taking ICS may be beneficial in dealing with virusinfections, specifically those due to coronavirus. Pre-treatment of human respiratory epithelial cellsin vitro with budesonide, in combination with glycopyrronium and formoterol, has inhibitory actionson coronavirus HCoV-229E replication and cytokine production(22). Furthermore, early, not yetpeer-reviewed data, suggest ciclesonide blocks SARS-CoV-2 ribonucleic acid replication in vitro (23)and inhibits SARS-CoV-2 cytopathic activity (24) which may be of great relevance to reducing the riskof developing of COVID-19 in response to SARS-CoV-2 infection or reducing the severity of thedisease.ICS use undoubtedly reduces the rate of exacerbations in both asthma and COPD. If people withstable asthma stop or reduce their ICS inappropriately in response to concerns aboutimmunosuppression and worries about developing COVID-19, they may be at significant risk ofhaving an exacerbation. Approximately 40–60% of COPD and up to 80% of asthma exacerbations are due to viral infections, including common coronaviruses (25). Therefore, the use of ICS must either reduce the risk of becoming infected or modify the subsequent inflammatory response and lungdamage. In vitro, corticosteroids inhibit rhinovirus and respiratory syncytial virus induced cytokinerelease . But the timing of exposure to ICS appears important with pre-treatment less effectivethan administration at the time of infection (26)

Pertaining to the efficacy of N-acetylcysteine it was found that NAC a thiol reducing agent, has mucolytic properties of degrading the disulfide bonds (S–S) to a sulfhydryl bond (–SH) in mucoprotein complexes that no longer cross-linking.And it may also reduce the mucus elasticity and viscosity and facilitate the removal of pulmonary secretions.[27] Moreover, it prevents bacterial stimulation of mucin production and mucus hyper-secretion[28]NAC exhibits direct as well as indirect antioxidant properties. Its direct effect is due to a free thiol group interacting with and scavenging ROS.[29]Its indirect antioxidant effect is related to its role as glutathione (GSH) precursor, resulting in increase of intracellular GSH concentration.

Using inhalational budesonide and intravenous N acetyl cysteine as an adjuvant therapeutic agents to the standard regime for suspected covid 19 induced pneumonia resulted in improving the oxygen saturation and overall respiratory indices .This helped in prevention of need of invasive mechanical ventilation and its associated complications.This also aided in awake prone ventilation and its benefits.Also prevention of oxidative injury to other system helped in overall better outcome of the patients.

CONCLUSION:

Use of inhalational budesonide and intravenous N acetyl cysteine along with the standard therapeutic protocol for suspected covid 19 induced pneumonia results in improvement of oxygen saturation in early phase .

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