Journal of Research in Medical and Dental Science
2022, Volume 10, Issue 8, Page No: 105-109

Available Online at: www.jrmds.in
eISSN No. 2347-2367: pISSN No. 2347-2545

Effect of Dexamethasone in Hospitalized Covid-19 Patients-Preliminary Report

Sakshi Sharma, Lokesh Vaishnav, Abhishek Joshi*, Ashok Mendhale

Department of Community Medicine, Datta Meghe Institute of Medical Sciences (Deemed University), India

ABSTRACT

Introduction: Covid19 is a viral disease caused due to Severe Acute Respiratory Syndrome Coronavirus 2 . It causes mild to moderate lung damage.. Most of the patients are either presenting with no symptoms or with mild symptoms but there are some patients who presented with severe lung damage and needed hospitalization. Severe covid 19 is marked by inflammatory organ injury. The use of Corticosteroids helped in suppressing inflammation and reduced chances of landing in respiratory failure.

Method: The trial referred to as RECOVERY (Randomized Evaluation of COVID-19 Therapy) which is controlled, randomized, open trial was performed in which 6mg dexamethasone was randomly given once daily to the patients for ten days and was then compared to the patients given basic care only. The 28-day mortality was reduced as a result.

Result: 4321 patients were randomly selected for usual care treatment whereas 2104 patients were treated with dexamethasone. As a result, about 1065 (24.6%) patients on usual care and 454 patients with dexamethasone died within 28days. The reduction in mortality rate varied based on the respiratory support level at randomization. It was observed that in patients receiving dexamethasone along with invasive mechanical support; mortality rate reduced by one-third whereas it was reduced by 1/5th in patients given oxygen with mask and no decline was noticed in patients without any mechanical ventilation at randomization.

Conclusion: Dexamethasone was found to reduce 28-day mortality in patients hospitalized with covid-19 who were getting either invasive mechanical ventilation or oxygen alone at the time of randomization but not in those who were not receiving any respiratory support.

Key words: Dexamethasone, Randomized trial, Corona virus disease

HOW TO CITE THIS ARTICLE: Sakshi Sharma, Lokesh Vaishnav, Abhishek Joshi, Ashok Mendhale, Effect of Dexamethasone in Hospitalized Covid-19 Patients-Preliminary Report, J Res Med Dent Sci, 2022, 10 (8): 105-109.

Corresponding author: Abhishek Joshi

e-mail✉: drabhijo19@gmail.com

Received: 13-July-2022, Manuscript No. JRMDS-22-69183;

Editor assigned: 15-July-2022, **PreQC No.** JRMDS-22-69183(PQ);

Reviewed: 29-July-2022, QC No. JRMDS-22-69183 (Q);

Revised: 04-August-2022, Manuscript No. JRMDS-22-69183 (R);

Published: 11-August-2022

INTRODUCTION

SARS-CoV-2 is a coronavirus that causes severe acute disease affecting lungs. The most of the cases of Covid19 are without any symptoms or show just minimal symptoms. It was discovered in end of 2019 in china that it was being spread by a zoonotic source [1]. However, a respiratory problem requiring hospitalization occurs in a significant number of patients [2], and such infections might result in serious illness needing ventilator support due to hypoxemia [3-6]. Patients with Covid19 being hospitalized in hospitals in the UK in the initial months of 2020 had a case fatality rate of overall 26% , and 37% and more for those who required mechanical ventilation by invasive methods [7].

Despite the fact that remdesivir has been shown to reduce mortality in hospitalized patients [8], no other therapeutic medicines have been found to have the same effect.

An acute episode of pneumonia along with widespread opacity witnessed on radiological examination and on autopsy alveolar destruction, infiltrates suggestive of inflammation and thrombotic changes in microvasculature are the pathophysiological characteristics of severe Covid19 [9]. In several pneumonias caused by viruses such as H5N1 influenza [10], SARS [11], and pandemic and seasonal influenza [12], the immune response by the host has played a critical role in the pathogenesis of failure of organs. Patients with severe Covid19 may have inflammatory

organ damage, and in that there is patients' subgroup who has markedly raised levels of inflammation markers such as C reactive protein, IL-1, ferritin, and IL-6 [6,13,14]. Various treatment strategies were recommended to reduce inflammation to organs in pneumonia caused by viruses, however the effectiveness of corticosteroids (glucocorticoids) is being questioned [15,16]. Although one small study revealed that patients suffering from Covid-19 who were prescribed methylprednisolone had improved clinical results [17], the absence of authentic data from huge-scale randomized trials casts doubt on the steroids' efficacy in Covid-19 patients. Glucocorticoids have been proposed as contraindicated or not encouraged in several treatment guidelines for these people, despite the fact that they are administered for severe instances in China [18]. Glucocorticoids were given to up to 50% of patients in various studies during the first six months of the disease, indicating that practice varied considerably throughout the world [19,20]. The outcomes of the RECOVERY (Randomized assessment of Covid-19 Therapy) study of dexamethasone in Covid-19 patients are discussed.

Objective

To detect dexamethasone's efficacy in lowering 28 day death rate in hospitalized patients suffering from COVID19 along with use of external ventilator support.

METHODS

Trial design

The study named as RECOVERY, which was financed by the National Institute for Health Research Clinical Research Network, intended to assess the efficacy of various therapies in patients hospitalized with Covid19 at total of 176 NHS hospitals all over the United Kingdom.

According to the attending physician, hospitalized patients who had clinically suspected or laboratory confirmed cases of SARS-CoV-2 infection without any past medical history that would place them at high risk if at all they participated were eligible for the study. In the starting, patients who were 18 years old were considered, however that restriction was lifted on 9th may last year. Pregnant women or women who were breastfeeding were also included in the study. All patients provided written informed consent or a legal representative provided consent if they were not able to do so.

Randomization

The trial-group assignment was masked by using a Web-based randomization technique. Patients who were qualified and volunteered after taking consent were randomly being put to one among the three groups: basic care alone, basic care plus dexamethasone 6 mg once in a day for 10 days given orally or intravenously, or another of the relevant and available drugs being studied in the study.

Procedure

The local study staff was to fill out an online form for follow up after each and every patient who was either discharged or passed away, or 28 days following random selection, whichever appear first. Patients' compliance with their prescribed therapy, other medications receipt given for covid 19 management, no of days stay in the hospital, assistance in breathing (type and duration), dialysis due to renal failure or hemofiltration, and vital condition were all noted (also includes the death cause). Normal patient care and registered data, such as vital information (including date and cause of death), discharge from hospital and renal and respiratory support therapy, were also obtained.

Outcome measures

The initial endpoint was death from any cause in 28 days of random selection, with six-month follow-up analyses. Secondary endpoints were delay to be released out of the hospital and, in patients who had not been ventilated mechanically by invasive means during the time period of randomization, following ventilation by invasive means or death of the patient. Other clinical results were death due to specific cause , renal failure leading to dialysis or hemofiltration, severe arrhythmia due to cardiac complications (reported in a subset), and ventilation received . The result of effective discontinuation of ventilation by invasive means was characterizes as stoppage upto (and survival to) 28 days among individuals undergoing ventilation mechanically by invasive means during the period of random selection.

Analysis to statistics

As indicated in the above mentioned protocol, while the experiment was being designed at the outset of the Covid-19 epidemic, suitable sample quantities were not able to be calculated. The study steering group predicted that if 28-day death rate was 20%, recruiting at least 2000 patients on dexamethasone and 4000 patients with only usual care would offer power of 90% at a two-sided P value of 0.01 to detect a clinically significant proportionate reduction of 20%. (a 4 percentage point difference in absolute terms).

As a result, on 8th of June, 2020, steering committee decided to halt recruiting patients for the dexamethasone group because the patient count had reached 2000.For the first outcome of mortality within 28days, the death rate ratio was being determined by using the hazard ratio from Cox regression. To illustrate overall deaths during the period of 28 days, Kaplan-Meier curves of survival were developed.

The secondary conclusion of discharge from hospital after 28 days and the result of effective termination of respiratory aid given invasively were also been taken into account and checked with the help of Cox regression. On 29th day, data for the patients who during their stay died were suppressed for both of these outcomes.

Because the precise date of ventilation by invasive means was not available for the already specified secondary outcome of invasive ventilation or 28 days mortality (in the patients who were not getting ventilation

by invasive means during random selection), a log binomial regression model was being used to identify the risk ratio. Age, gender, race, respiratory assistance required, days from when illness start and anticipated 28-day death risk were all taken into consideration. Were utilized to split the subjects into six categories based on randomization characteristics: age, gender, race, respiratory aid, days since symptom arise, and the likelihood of death in the next 28 days.

We used regression models with an interaction between the treatment workups and the subgroup of choice to obtain risk ratios (or rate ratios in some of the trials) and associated confidence intervals in prespecified subgroups.

The subgroup specific log estimates were then subjected to Chi-square tests for heterogeneity or linear trend, as per the method. All of the hypothesis was conducted with an intention to treat patients. The trial team controls the whole database, which was compiled from trial sites and analyzed at the University of Oxford's Nuffield Department of Population Health.

RESULTS

Patients

9355 individuals (83%) in total were qualified to get dexamethasone out of 11,303 that were randomly assigned between March 19 and June 8, 2020. (i.e Dexamethasone had no recognized indications or contraindications for the patient.). 6425 patients in total had randomly been chosen to administer dexamethasone drug (2104 out of 6425 patients) or usual treatment only (4321 out of 6425 patients). The rest of all the patients had randomized at random to another therapy groups in the trial. The patients in this trial had mean (SD) age of 66.±15.7 years, with 36% of patients being females. 24% of the patients presented with diabetes, 27% with heart disease, and chronic respiratory disorder was present in 21%,along with 56 percent of the patients presenting with at least 1 significant comorbid ailment. During the time of randomization, 16 percent patients had been provided with ventilation by invasive means or membrane oxygenation extracorporeal, 60 percent were given oxygen exclusively (with noninvasive ventilation or without it), and 24 percent were given none of them.

Primary outcome

After 28 days, the glucocorticoids group had a much decreased death rate than the other group receiving just standard treatment, with 482 patients out of the 2104 in total (22.9%) and the rest 1110 out of the 4321 patients (25.7%) dying, respectively. There was a propensity in a prespecified trial to show the largest absolute and proportional benefit among those undergoing ventilation by invasive means, depending on the degree of respiratory help they were getting at randomization. Patients getting ventilation mechanically by invasive means and those receiving oxygen not with the help of invasive ventilation had a reduction in number of deaths in the group given dexamethasone in comparison to the other group given normal care alone. No discernible effect on patients with dexamethasone and without getting any respiratory aid during the period of randomization was observed. Patients having a longer history of symptoms (and mostly who were be on mechanical ventilation by invasive methods during the randomization time) had a higher mortality benefit from dexamethasone treatment. Dexamethasone was observed to be associated with lower 28day mortality rate among individuals with symptoms lasting for 7 days or more, but not in those who had symptoms more recently.

Secondary outcomes

Patients given dexamethasone has less hospital time recorded and were mostly be sent home from hospital in 28 days in comparison to the normal care ones. Patients given ventilation by invasive methods during random trials had the largest impact on getting patients out of the hospital in 28 days' time period. All of the patients who proceeded to the already established composite secondary objective of ventilation by invasive means or death were less in the patients administered dexamethasone as compared to the patients who do not get any glucocorticoids during the time of random selection. Individuals who were getting oxygen during randomization saw a greater impact.

The most common cause of mortality was Covid-19, which was less common in the group given dexamethasone in comparison to the basic care patients. The dexamethasone patients and the basic care ones both had equal rates of mortality from other causes. The incidence of new cardiac arrhythmia was same in the patients administered with dexamethasone and the other group with only usual care in the subset of the patients with accessible data. Authors found four cases of major side effects associated with dexamethasone: 2 cases of raised blood sugar, 1 case of GI bleeding, and 1 case of psychosis (all of these are recognized side effects of corticosteroids).

DISCUSSION

Dexamethasone administered for 10 days to hospitalized patients having Covid19 has helped in decreasing 28day death rate in patients with basic care who were getting ventilation by invasive means during the randomization time and the ones receiving oxygen only and not any other sort of ventilator aid, according to preliminary findings. However, no evidence has been traced about dexamethasone being helpful to patients that were not getting breathing help at the time of randomization, and the data pointed to possible damage in this group. Patients who were given treatment for 7 days or more after the symptoms arise, when lung damage due to inflammatory changes was more likely, had a benefit as well. After 60 days, mortality was reduced to 15 percentage points in the patients given dexamethasone in comparison to the control group in the previous trial

including patients having severe distress syndrome causing breathlessness and were on ventilator, a finding that resembled our findings.

The study named RECOVERY was made to give a quick and reliable evaluation about the efficacy of immediately available prospective Covid19 therapies on 28day death rates. The trial enrolled fifteen percent of total hospitalized Covid19 patients in UK, and death in the group with normal care was comparable to overall death cases of patients being hospitalized because of Covid19 [7]. Only the most basic information was gathered at hospital locations, and extra information (such as longer-term mortality) obtained by linking data with regular sources. Physiologic, laboratory, and virologic measurements were not obtained. The protocol blends techniques employed in the large, straightforward trials of medications for acute Ischemic heart disease during the 1980s with the possibilities offered by newer health care techniques in the 2020s [21-25]. This trial had advanced quickly, which was critical for epidemiological investigations [26]. These primary dexamethasone results were released on 16th of June 2020, approximately 100 days from the establishment of protocol and were taken up by the UK into practice the same day [27].

Glucocorticoids have been used to treat severe acute lung disorders, Middle East respiratory disease (MERS) and influenza, and CAP, all of which are linked to Covid-19. However, the proofs supporting or forbidding the usage of dexamethasone in those instances have been poor due to insufficient data from suitably powered randomized, controlled research [28-31]. Moreover, variation has been noticed in dosages of glucocorticoids, disease severity and medical issues, causing the evidence base to be harmed. The favorable benefits of glucocorticoids in severe viral infections affecting the lungs are most likely dependent on the precise dose being administered to the correct patient at the right time. Large dosages and the medications given during a time period when replication of virus is maximum with minimal inflammation have proven to be damaging and not helpful. The Patients suffering from influenza, MERS and Severe acute respiratory illness was given systemic glucocorticoids had showed slower viral RNA clearance. Clinical significance of such findings is still not known [29,32,33]. In contrast to SARS, when replication of virus reaches its peaks in 2nd week of sickness [34], SARS-CoV-2 shedding of virus seems to be at peak early in the disease and then falls [35-38]. Dexamethasone provides a larger mortality benefit in Covid19 patients having respiratory aid and who are recruited within the 1st week of the disease, indicating that immunopathological aspects may be dominating at that point, with active viral replication influencing later. This theory implying dexamethasone's effectiveness in patients with corona virus illness should not be generalized to other individuals with viral-induced respiratory infections having a different symptomatology.

Recovery research demonstrates that patients suffering from Covid-19 and getting respiratory aid in addition to dexamethasone with a dosage of 6 milligram once in a day for at least 10 days had a lower 28day death rate. Those who need not require oxygen had shown no improvement (and the potential for damage). A lot of treatment instructions for covid 19 quoted that the usage of dexamethasone was prohibited and not suggested until the investigation was completed [18]. In WHO's list of essential medications, dexamethasone is mentioned and is widely available at a cheap cost around the world. The National Institutes of Health in the United States and the Chief Medical Officers in United Kingdom have changed their guidelines already to suggest the inclusion of glucocorticoids in Covid-19 patients treatment protocol who have been admitted to the hospital [27,39].

CONCLUSION

Coronavirus disease 2019 is a severe respiratory disorder causing damage to lungs. During the pandemic when so many drug trails were going on it was found that Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death.

So Dexamethasone trails were done on hospitalized patients who were either getting mechanical ventilator support by invasive means or oxygen alone or no support at all and It was found out that Dexamethasone was able to reduce 28-day mortality in patients hospitalized with covid-19 who were getting either invasive mechanical ventilation or oxygen alone at the time of randomization but not in those who were not receiving any respiratory support.

REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382:727-733.
2. Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: A model-based analysis. Lancet Infect Dis 2020; 20:669-677.
3. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020; 395:1054-1062.
4. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020; 395:507-513.
5. Cao J, Tu W-J, Cheng W, et al. Clinical features and short-term outcomes of 102 patients with corona virus disease 2019 in Wuhan, China. Clin Infect Dis 2020; 46:851-853.
6. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020; 46:846-848.

7. Docherty AB, Harrison EM, Green CA, et al. Features of 20,133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical characterization protocol: Prospective observational cohort study. BMJ 2020; 369:m1985-m1985.
8. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—preliminary report. N Engl J Med 2020; 383:1813-1836.
9. Carsana L, Sonzogni A, Nasr A, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: A two-centre descriptive study. Lancet Infect Dis 2020; 20:1135-1140.
10. de Jong MD, Simmons CP, Thanh TT, et al. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. Nat Med 2006; 12:1203-1207.
11. Wong CK, Lam CWK, Wu AKL, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol 2004; 136:95-103.
12. Baillie JK, Digard P. Influenza—time to target the host? N Engl J Med 2013; 369:191-193.
13. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395:497-506.
14. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science 2020; 368:473-474.
15. Shang L, Zhao J, Hu Y, et al. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet 2020;395:683-684.
16. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020; 395:473-475.
17. Corral L, Bahamonde A, Arnaiz de las Revillas F, et al. Glucocovid: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. MedRxiv 2020.
18. Dagens A, Sigfrid L, Cai E, et al. Scope, quality, and inclusivity of clinical guidelines produced early in the covid-19 pandemic: Rapid review. BMJ 2020; 369:m1936-m1936.
19. Zhao JP, Hu Y, Du RH, et al. Expert consensus on the use of corticosteroid in patients with 2019-nCoV pneumonia. Chinese J Tuberc Respir Dis 2020; 43:183-184.
20. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323:1061-1069.
21. Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: Retrospective case series. BMJ 2020; 368:m606-m606.
22. Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: A multicentre, randomised controlled trial. Lancet Respir Med 2020; 8:267-276.
23. Yusuf S, Collins R, Peto R. Why do we need some large, simple randomized trials? Stat Med 1984; 3:409-422.
24. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; 2:349-360.
25. Collins R, Bowman L, Landray M, et al. The magic of randomization versus the myth of real-world evidence. N Engl J Med 2020; 382:674-678.
26. Rojek AM, Horby PW. Modernizing epidemic science: Enabling patient-centred research during epidemics. BMC Med 2016; 14:212-212.
27. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103054
28. Stockman LJ, Bellamy R, Garner P. SARS: Systematic review of treatment effects. PLoS Med 2006; 3:e343-e343.
29. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. Am J Respir Crit Care Med 2018; 197:757-767.
30. Lansbury LE, Rodrigo C, Leonardi-Bee J, et al. Corticosteroids as adjunctive therapy in the treatment of influenza: an updated Cochrane systematic review and meta-analysis. Crit Care Med 2020; 48:e98-e106.
31. Siemieniuk RA, Meade MO, Alonso-Coello P, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: a systematic review and meta-analysis. Ann Intern Med 2015; 163:519-528.
32. Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients. J Clin Virol 2004; 31:304-309.
33. Lee N, Chan PKS, Hui DSC, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. J Infect Dis 2009; 200:492-500.
34. Cheng PKC, Wong DA, Tong LKL, et al. Viral shedding patterns of coronavirus in patients with probable severe acute respiratory syndrome. Lancet 2004; 363:1699-1700.
35. To KKW, Tsang OTT, Leung WS, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: An observational cohort study. Lancet Infect Dis 2020; 20:565-574.
36. Zhou R, Li F, Chen F, et al. Viral dynamics in asymptomatic patients with COVID-19. Int J Infect Dis 2020;96:288-290.
37. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med 2020; 26:672-675.
38. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020; 581:465-469.
39. https://www.covid19treatmentguidelines.nih.gov/dexamethasone/