International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 1266-1276 www.ijprajournal.com ISSN: 2249-7781

Effectiveness of Dexamethasone and Methylprednisolone in Covid-19 Patients

Dr. K. Jayaprakash[1],M. Rangapriya[2]* M. Karthika[2], Nancy Sinha[2]
Consultant Anaesthetist, Vivekanandha Medical Care Hospital
Department of Pharmacy Practice, SwamyVivekanandha College of Pharmacy, Tiruchengode,Tamilnadu, India.

Date Of Submission: 01-03-2021 Date Of Acceptance: 14-03-2021

ABSTRACT: Background: The coronavirus disease 2019 (COVID-19) which emerged in China is the major cause for severe acute respiratory syndrome. MostlyCOVID-19 infections are either asymptomatic or mild. The symptomatic will be hospitalized and supplemented with oxygen along with other treatment strategies. Viral replication may interfere with the inflammatory markers and can cause cytokine storm. The present study was done to estimate the efficacy of dexamethasone and methylprednisolone usage against the COVID-19 infection on high resolution oxygen saturation and to determine their relationship with inflammatory markers and duration of hospital stay.**Methods**: 38 medical records were collected for this retrospective quasi-experimental study using appropriate sampling methods and divided into two groups of 19 patientseach. Group A were treated with dexamethasone 6 mg once daily and Group B with methylprednisolone 40mg twice daily. The assessment included the level of inflammatory markers, oxygen saturation before and after administering the drugs and also the duration of hospital stay after treating with the drugs. **Results:**Demographic findings showed that the male patients (65.78%) were predominant over females (30.77%)and the mean age of the participants was 59.6 years. Dexamethasone administration proved to be effective in improving the oxygen saturation level to 97.7% andreducedduration of hospital stay (8days) when compared to methylprednisolone (10days).**Conclusion:** Steroids has anti-inflammatory ability to treat against COVID-19 infection. Dexamethasone showed a higher efficacy rate with a positive outcome towards quality of life in the particular study population.

I. INTRODUCTION

The coronavirus disease 2019 (COVID-19) emerged from zoonotic source belonging to the coronaviridae family in China from the town of Wuhan is the cause for severe acute respiratory syndrome possessing the alarming symptoms of a pandemic crisis.[1,2]Most COVID-19 infections are either asymptomatic or result in a mild illness.[3]With symptomatic care, a patient with mild illness may be treated at home.Patients with the moderate illness need hospitalization and oxygen supplementation along with other treatment strategies.[4] However, olderindividuals and those with comorbidities may develop a serious illness that causes hypoxemic respiratory failure requiring extendedventilatory supportand intensive care.[5,6]

Around 19% of patients undergo an uneventful recovery, while 14% of patients show progressive worsening leading to severe pneumonia and critical pneumonia in 5% of patients.[7,8]

The acute respiratory distress syndrome (ARDS) typically progresses from the second week. This is not only due to unregulated viral replication but also because of the host's explosive immune response. The presence of uncontrolled viral replication, an increased number of infected epithelial cells and cell debris induces massive cytokine release named "cytokine storm"along with hyper inflammation and immune suppression characterized by a decline in CD4-β T helper cells memory and increased CD8 cytotoxicity.[9]

Severe COVID-19 can cause inflammatory organ injury and a subset of patients are identified with markedly elevated inflammatory markers such as C-reactive protein, ferritin, and interleukins (IL-1 and IL-6).[10,11]The "cytokine storm" leads to major vascular inflammation,
disseminated coagulation, shock, and hypotension r esulting in multiorganfailure and death.[12]SARS-COV-2 infection causesthe high morbidity and mortality associated with the autoimmune degradation of the lungs induced by the release of a storm of pro-inflammatory cytokines.[13]Research has shown that any intervention capable of avoiding this catastrophe (cytokine storm) can also

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 1266-1276 www.ijprajournal.com ISSN: 2249-7781

preventlung damage (ARF) and pulmonary thromboembolism. This pathophysiology was taken into account in COVID-19 while intervening with corticosteroids.[14]

Corticosteroids are potent anti-inflammatory drugs that can promote ARF resolution in severe COVID-19 infectionpatients.[15] Previously, corticosteroids have been used in respiratory illnesses like asthma, COPD, severe bacterial pneumonia, and acute respiratory distress syndrome.[4] The extended use of low-dose corticosteroid has been recently reviewed in severe COVID-19.A major study conducted in Michigan reported a positive outcome of early treatment with a short course of steroids.[16]

Some studies demonstrated a strong response to steroids by reducing inflammation.[17,18] However the use of corticosteroidsisstill controversial in COVID-19 disease.[4]Thepatient's immunity is weakened by corticosteroids which make them more vulnerable to superimposed infections.[19]Since corticosteroids contribute to immune suppression, they are largely discouraged by the fear of worsening the viral propagation due to impaired innate immunity.However, there is no increased incidence of severe or critical pneumonia in patients with long term steroid therapy.[14]Interestingly, most of theprevious research in SARS-COV-1 and MERS-COVreported adverse outcomes with corticosteroid therapy.[20,21} Two recent comments in the Lancet have shown that corticosteroids for the treatment of COVID-19should be avoided. However, these conclusions are focused primarily on observations with related viral diseases but not explicitly COVID-19.[22,23]

A randomized clinical trial found that corticosteroid therapy could minimize inflammatory responses, treatment failure, and clinical stability without significant adverse effects in community-acquired pneumonia.[24]Improvement in clinical symptoms and oxygenation in severe COVID-19 patients through corticosteroid therapy were reported in clinical practice.[25]The study conducted by Wang et al. also reported that corticosteroid therapy reduced length of hospital stay and intensive care in severe COVID-19 patients.[17]Chinese experts revealed that it is wise to administer short courses of corticosteroids at low-to-moderate doses in critically ill COVID-19patients.[23]

TheWorld Health Organization (WHO) and The Center for Disease Control and Prevention (CDC), USA also provide special adviceon the utilization of corticosteroids in COVID-19 for immune modulation purpose.[24,25]

The recent multinational surviving sepsis guideline for COVID-19, recommends that steroids may be given to patients with severe COVID-19 with mechanical ventilation and ARDS to scale back the destructive inflammatory immune reaction and to treat suspected adrenal insufficiency associated with septicemia, particularly with refractory shock.[28]

OBJECTIVE

Steroid usage in moderate to severe patients is a standard practice in COVID 19 and we have been practicing the same. Some of the cases were given dexamethasone while others were given methyl prednisolone.

The primary objective of the study was to assess the efficacy of dexamethasone and methylprednisolone in the COVID 19 patients in respect to oxygen saturation, level of inflammatory marker and the duration of hospital stay.

HYPOTHESIS

Two hypotheseswere created: H1 (alternate hypothesis) and the H0 (null hypothesis). The H1 hypothesis states that dexamethasone and methyl prednisolone are effective in the treatment of moderate to severe COVID patients and H1 hypothesize that dexamethasone and methyl prednisolone are not effective in the treatment of moderate to severe COVID patients.

II. MATERIALS AND METHODS

A retrospective quasi experimental study designwas used to assess the efficacy of dexamethasone and methylprednisolone in COVID 19 patients. All data were collected from the medical records by maintaining proper sampling technique. The records of 38 patients who were admitted and treated in the COVID ward atVivekanandha Medical Care Hospital, Tiruchengode, TamilNaduwas collected with the approval of the Institutional Ethical committee (SVCP/IEC/JAN/2021/12). Patients were included on the basis of CT severity index (8-16 out of 25) and non-invasive ventilator support.Thesepatients were divided into twogroups: Group-1 underdexamethasone 6mg once dailyand Group - 2 who received Methylprednisolone 40mg twice daily. Laboratory investigations were collected to evaluate the inflammatory markers and similarly the oxygen saturation level was checked on daily

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 1266-1276 www.ijprajournal.com ISSN: 2249-7781

basis. Data were evaluated through Microsoft Excel sheet using descriptive statistics.

III. RESULTS

The study observations on the efficacy of dexamethasone and methyl prednisolone are presented in regard to different sections. Section 1 includes demographic characteristics of COVID patients. Section 2 predicts the changes in laboratory profile in relation with dexamethasone and methylprednisolone. Section 3 interprets the effectiveness of both the drugs.

SECTION 1

The mean age of the study participants was observed to be 59.6years (Figure 1). Age wise distribution showed that nearly 35.89% and 26.32% of participants belonged to the age interval of 51-60 years and 61-70 years respectively.

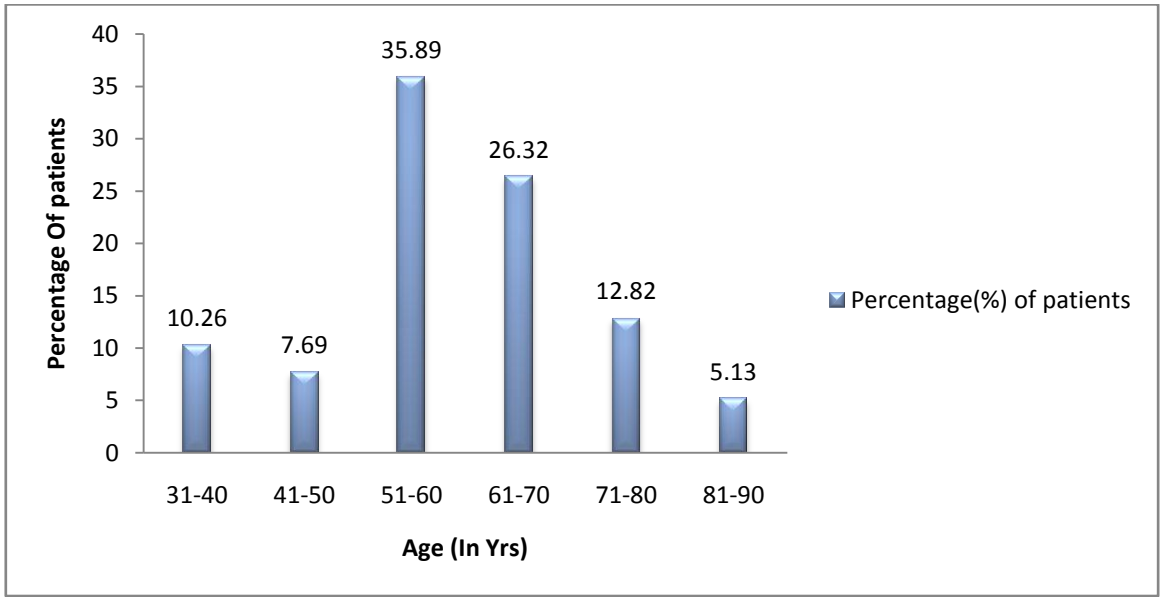

FIGURE-1: AGEWISE DISTRIBUTION (n=38)

Male patients were affected more (65.78%) when compared tofemales 33.33%(Figure-2).

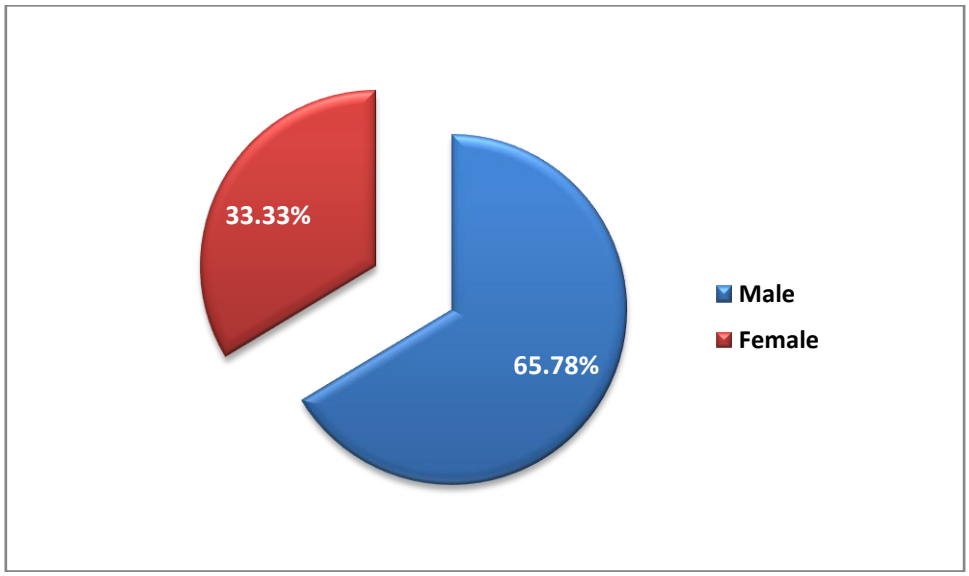

FIGURE-2: GENDERWISE DISTRIBUTION OF PATIENTS (n=38)

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 1266-1276 www.ijprajournal.com ISSN: 2249-7781

68.42% of the patients suffered a co-morbid condition and 30.77% were devoid of comorbidity. A history of hypertension was found in majority of patients (39.47%), diabetes in 28.21%, 13.15% suffered CAD and 12.82 reportedbronchial asthma while the remaining patients (17.95%) showed other co-morbid conditions like CVA, hypothyroidism, hyponatremia, UTI and GERD.

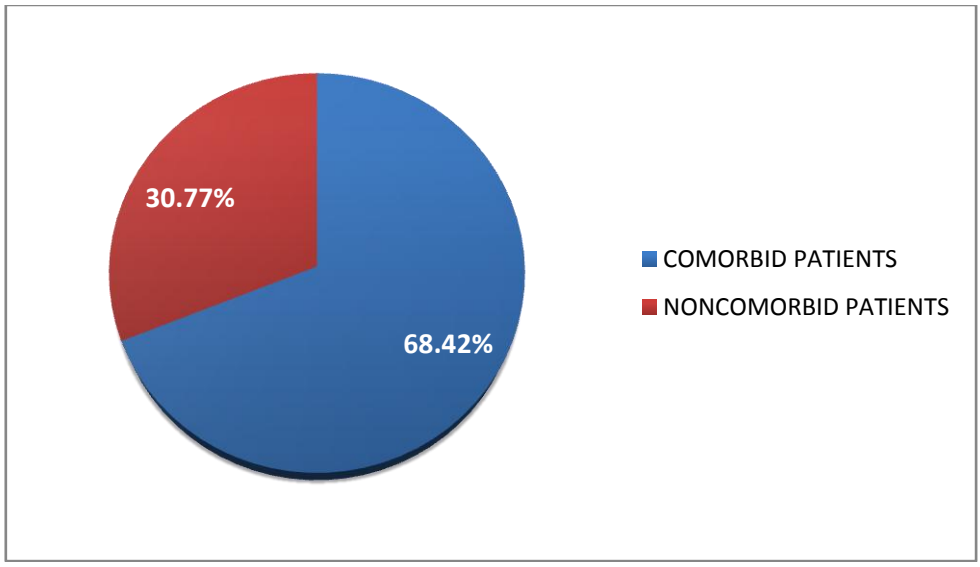

FIGURE-3: COMORBID CONDITIONS AMONG COVID PATIENTS

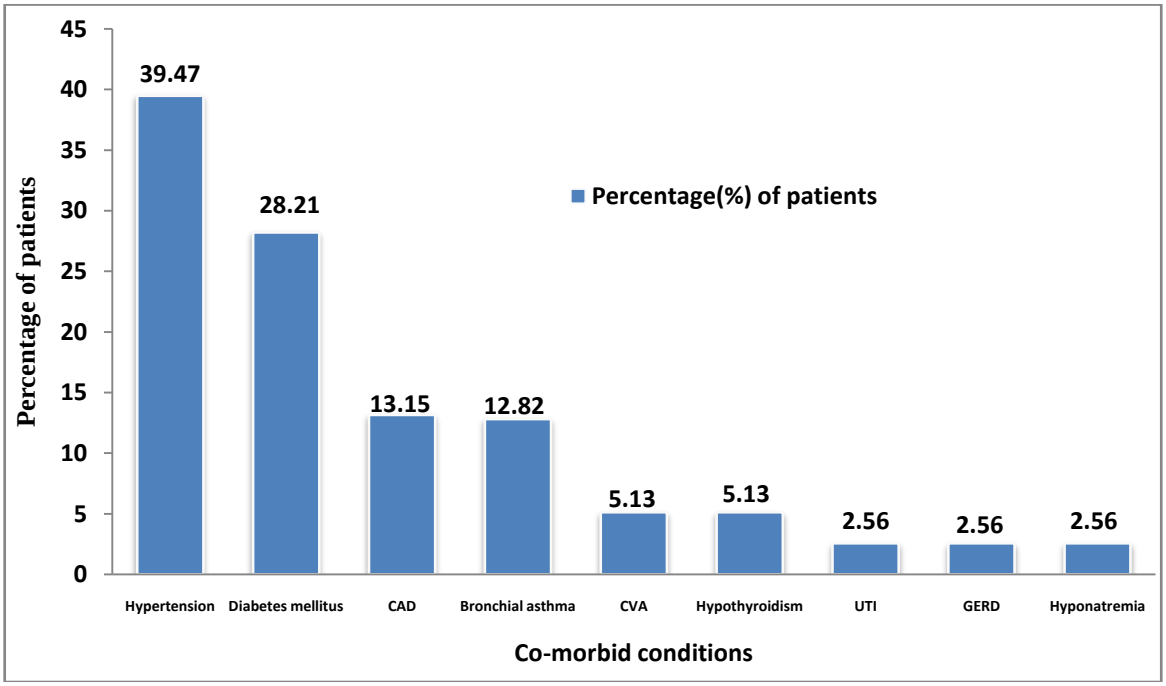

FIGURE-4: CATEGORIZATION OF COMORBID CONDITIONS

Data from the medical records confirms that all the patients were symptomatic and the most common symptoms were found to be fever (89.47%), cough/cold (68.42%), myalgia (71.05%), breathing difficulty (66.67%), headache (33.33%), sore throat (28.94%) and other symptoms (73.68%) like nausea, vomiting, dysgeusia, diarrhea, anosmia and tiredness (Figure 5).

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 1266-1276 www.ijprajournal.com ISSN: 2249-7781

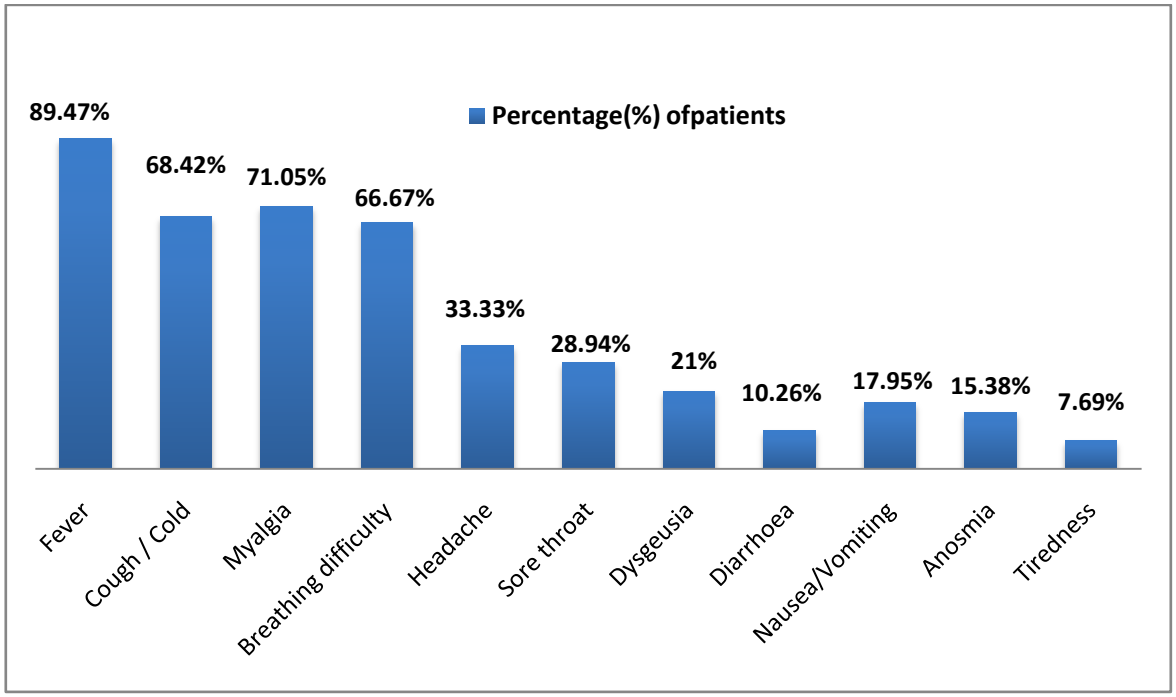

FIGURE-5: CLINICAL MANIFESTATION AMONG COVID-19 PATIENTS

SECTION 2

The study population was divided into two groups. Group A comprised of patients who received dexamethasone 6mg/day intravenously and Group B treated with methylprednisolone 40mg BD intravenously. In this analysis, thelaboratory report (Table-1) showed that the initial mean CRP in group A was 5.25 mg/L which reduced to 3.37 mg/L after the therapy. Similarly, the CRP in group B was 5.06 mg/L and reduced to 4.73 mg/L after the therapy.

Table-1: C-reactive protein before and after steroid therapy

Group	**No.of patients** (n=38)	**MEANCRPLEVEL** Before therapy **(**mg/L)	**MEANCRPLEVEL** After therapy **(**mg/L)
Group A	19	5.25	3.37
Group B	19	5.06	4.73

The initial mean ferritin level in group A was within normal range of31.96 ng/ml and 41.39ng/ml after the administration of dexamethasone. Similarly in the case of methylprednisolone, the initial level of mean ferritin level was57.91ng/mland 61.52ng/ml after methylprednisolone administration (Table-2).

Table-2: Ferritin level before and after steroid therapy

Group	**No.of patients** (n=38)	**MEANFerritin LEVEL** Before therapy **(**ng/ml)	**MEANFerritin LEVEL** After therapy **(**ng/ml)
Group A	19	31.96	41.39
Group B	19	57.91	61.52

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 1266-1276 www.ijprajournal.com ISSN: 2249-7781

The LDH level was also monitored. The initial mean LDH in the group A was 118.27 U/L which decreased to 153.80 U/L , but the initial mean of LDH in group B was 240.29 U/L which decreased to 268.07 U/L after the administration of methylprednisolone. (Table-3)

Table-3: LDH before and after steroid therapy

Group	**No.of patients** (n=38)	**MEANLDHLEVEL** Before therapy (U/L)	**MEANLDHLEVEL** After therapy (U/L)
Group A	19	118.27	153.80
Group B	19	240.29	268.07

The D-Dimer level was also assessed and the report showed that the initial mean of D-Dimer in the Group A was 116.51 IU/ml and 98.53 IU/ml after administration of dexamethasone. But the initial mean of D-Dimer in group B was 119.43 IU/ml which increased to144.01IU/mlafter administration of methylprednisolone. (Table-4)

Table-4: D-Dimer before and after steroid therapy

Group	**No.of patients** (n=38)	**MEAND-DimerLEVEL** Before therapy (IU/ml)	**MEAN D-DimerLEVEL** After therapy (IU/ml)
Group A	19	116.51	98.53
Group B	19	119.43	144.01

The IL-6 level was also assessed and the report showed that the initial mean of IL-6 in the Group A was 0.21pg/ml and 0.14pg/ml after administration of dexamethasone. But the initial mean of IL-6 in group B was 1.83 pg/ml before and1.73pg/mlafter administration of methylprednisolone. (Table-5)

Table-5: IL-6before and after steroid therapy

Group	**No.of patients** (n=38)	**MEANIL-6LEVEL** Before therapy (pg /ml)	**MEANIL-6LEVEL** After therapy (pg /ml)
Group A	19	0.21	0.14
Group B	19	1.83	1.73

The mean WBC level of group A wasinitially 4447.37cells/cummand increased to 6226.32cells/cumm. Similarly in group B there wasan elevation from 7780 cells/cummto 10093.33cells/cumm. (Table-6)

Table-6: WBC before and after steroid therapy

Group	**No.of patients** (n=38)	**MEAN WBC LEVEL** Before therapy (cells/cumm)	**MEAN WBC LEVEL** after therapy (cells/cumm)
Group A	19	4447.37	6226.32
Group B	19	7780	10093.33

Initially the mean lymphocyte level was10.84% which reduced to 8.89% in group A,similarly, the mean lymphocyte value of group B was also reduced from 15.33% to 15.2%. (Table-7)

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 1266-1276 www.ijprajournal.com ISSN: 2249-7781

Table-7: Lymphocyte before and after steroid therapy

Group	**No.of patients** (n=38)	**MEAN LYMPHOCYTE LEVEL** Before therapy (%)	**MEAN LYMPHOCYTE LEVEL** After therapy (%)
Group A	19	10.84	8.89
Group B	19	15.33	15.2

The initial mean level of neutrophil was 37.47% which increased to 50% after the administration of dexamethasone but in case of methyl prednisolone the initial mean 78.33% reduced to 77.33%. (Table-8)

Table-8: Neutrophil before and after steroid therapy

Group	**No.of patients** (n=38)	**MEAN NEUTROPHIL LEVEL** Before therapy (%)	**MEAN NEUTROPHIL LEVEL** After therapy (%)
Group A	19	37.47	50
Group B	19	78.33	77.33

In group A initial mean range of monocyte was 3.32% which was reduced to 2.79% after administering dexamethasone but in group B the initial mean value of monocyte was 4.66% which was increased to 5.33 % after administering methyl prednisolone. (Table-9)

Table-9: Monocyte before and after steroid therapy

Group	**No.of patients** (n=38)	**MEANMONOCYTE LEVEL** Before therapy (%)	**MEANMONOCYTE LEVEL** After therapy (%)
Group A	19	3.32	2.79
Group B	19	4.66	5.33

Before dexamethasone administration, the mean level of eosinophil was 1.42% which was reduced to 1.47% after the administration of dexamethasone. Similarly initial mean value of eosinophil was 2.33% which was reduced to 1.46 % after the administration of methylprednisolone. (Table-10)

Table-10: Eosinophil before and after steroid therapy

Group	**No.of patients** (n=38)	**MEANEOSINOPHIL LEVEL** Before therapy (%)	**MEANEOSINOPHIL LEVEL** After therapy (%)
Group A	19	1.42	1.47
Group B	19	2.33	1.46

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 1266-1276 www.ijprajournal.com ISSN: 2249-7781

The mean level of platelets in group A was 0.92 lakhs/cmm which was increased to 1.53lakhs/cmm. Similarly the platelet level in group B was 2.19 lakhs/cmm and increased to 2.73lakhs/cmm after the administration of methyl prednisolone. (Table-11)

Table-11: Platelet before and after steroid therapy

Group	**No.of patients** (n=38)	**MEANPLATELET LEVEL** Before therapy (lakhs/cmm)	**MEANPLATELET LEVEL** After therapy (lakhs/cmm)
Group A	19	0.92	1.53
Group B	19	2.19	2.73

SECTION-C

This section assessed the outcomes after administering dexamethasone and methylprednisolone. The SPO2 levels were monitored before and after administrationof the drugs. Dexamethasone improved the oxygen saturation level from 92.05% to 97.47% while in methylprednisolone the oxygen saturation level improved from 90.57% to 96.31%. In case of hospital stay, patients who received dexamethasone had a shorter period of stay (8days) as compared to methylprednisolone (10 days). This indicates dexamethasone minimized the duration of hospital stay more significantly than methylprednisolone. These outcomes confirm that dexamethasone showed more efficacy than methylprednisolone in the study population.

TABLE-12: SPO2 before and after steroid therapy

Group	**No.of patients** (n=38)	**MEAN SPO2LEVEL** Before therapy (%)	**MEAN SPO2 LEVEL** After therapy (%)
Group A	19	92.05	97.47
Group B	19	90.57	96.31

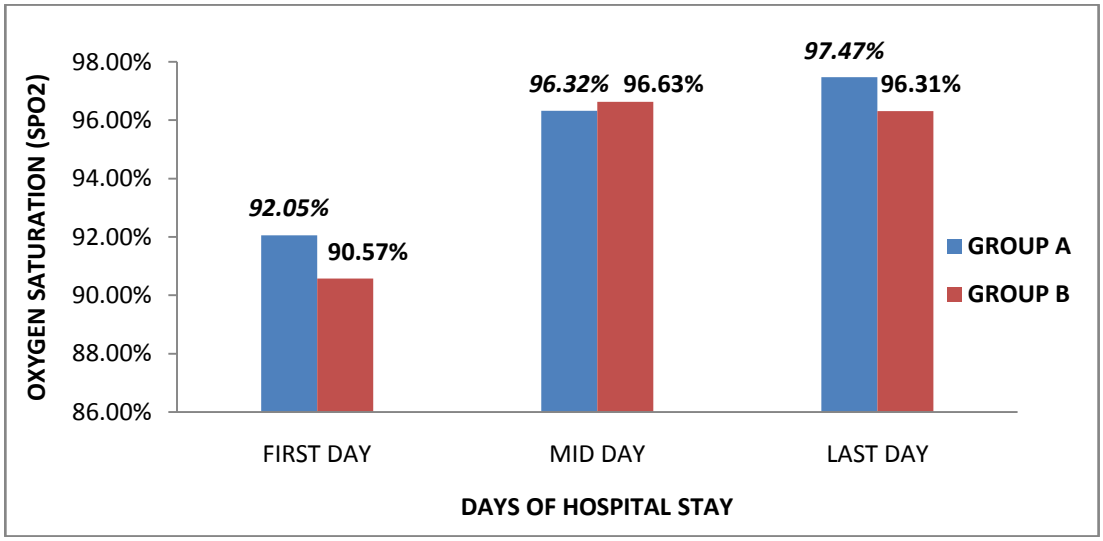

FIGURE-6: SPO2 before and after steroid therapy

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 1266-1276 www.ijprajournal.com ISSN: 2249-7781

IV. DISCUSSION

Our study is very relevant at the time of the COVID-19 pandemic. The use of two different corticosteroids in the treatment of moderate to severe covid disease was compared. There have been several studies on dexamethasone and methylprednisolone alone in the treatment of COVID-19. In our study, we selected 38 patients with moderate to severe COVID disease, who were divided into groups based on the steroids given. Group A consists of 19 patients receiving intravenous low dose dexamethasone 6mg/day and Group B consists of 19patients who were receiving intravenous methylprednisolone 40mg twice daily. More patients could not be enrolled due to the declining peak of COVID-19 and no further admissions with severe COVID-19 in our hospital.

The study participants in both groups had co-morbid conditions like hypertension, diabetes, CAD, CVA. The patients with comorbid conditions are more prone to ARDS due to the catastrophe called "cytokine storm". Hence we have selected these patients to assess the efficacy of dexamethasone and methylprednisolone in preventing the incidence of ARDS and reducing the mortality rate and hospitalization as well as in the improvement of oxygen saturation levels.

A similar standard of care was given to both groups including the use of antiviral, antioxidants and other symptomatic measures.

Dexamethasone, a broad-spectrum immune suppressor is a synthetic corticosteroid, which has a higher activity, longer half-life and duration of action than cortisone.[29,30]

The reason behind improved anti-inflammatory activity is that it decreases the gene transcription of several pro-inflammatory cytokines, chemokines, and adhesion molecules.[31]

Dexamethasone can be significant in patients with COVID-19 because of its ability to block the generation of cytokines and reduce their destructive effects. Hence, it is useful in counteracting the cytokine storm associated with COVID-19 patients.[30]Short-term dexamethasone therapy acts by inhibiting the severe cytokine storm or the hyper inflammatory phase thereby reduces the severity of inflammation in COVID-19patients who develop pneumonia.[32]

Some study findings support the dexamethasone usage in COVID-19 patients with hypoxemia, and therefore, the results should not be extrapolated to patients with the milder form of the disease.[33]

The recovery trial conducted in the UK proved the effectiveness of dexamethasone in COVID-19 patients. It was the largest trial conducted in the UK which reported that mortality rate was reduced in patients receiving dexamethasone than the standard group who expired within 28days of intervention.[34]

Our study results hadnegatively correlated with this report that out of 38patients, no patientdied in both the groups.

In severe viral respiratory infections, the beneficial effect of corticosteroids is dependent on the right dose, at the right time, in the right patient. Corticosteroid treatment in high doses can be more dangerous than its benefits, when control of viral replication is paramount and inflammation is minimal. It has been reported that there is a slower clearance of viral RNA in patients with SARS, MERS and influenza treated with systemic corticosteroids although their clinical relevance is unclear.[35-37]

In this study, the mean duration of hospitalization of the patients who were under oxygen supportwith dexamethasone and methylprednisolone were 8days and 10days respectively.

Recent reports found that early dexamethasone administration has minimized the duration of mechanical ventilation support and overall mortality rate for patients with moderate-to-severe ARDS.[38]

The randomized evaluation showed an improved outcome with dexamethasone in the treatment of severe COVID-19 requiring oxygen therapy.[39]

Hence in this study, it was observed that dexamethasone shortens the length of stay in hospital and showed earlier recovery, improves oxygen saturation level and reduces the severity of infection due to its improved bioavailability, longer duration of action, increased half-life and anti-inflammatory effects.

V. CONCLUSION

Steroids are well known anti-inflammatory drug used to reduce the exaggerated immune response named as "cytokine storm" in COVID-19 patients. Initial administration of low dose steroids, especially in patients who are prone to ARDS will help in improving the biochemical parameters and also reducesthe hospitalization of moderate to severe COVID-19 patients. In our study, Dexamethasone showed a higher efficacy

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 1266-1276 www.ijprajournal.com ISSN: 2249-7781

ratein the study population having positive outcomes such as reduced length of stay, oxygen saturation improvement and earlier discharge than in patients administered with methylprednisolone.

VI. LIMITATIONS

The major limitation of the study was thatmore number of patients could not be included in our study further as the conditionsettled down in the study site and there were no further admissions with severe COVID 19.Follow up was not done after the discharge of the patients from the hospital.

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.
[2]. Perlman S. Another decade, another coronavirus. N Engl J Med 2020;382:760–2.
[3]. 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(6): 669-77.
[4]. M. Cascella, M. Rajnik, A. Cuomo et al. Features, evaluation, and treatment of coronavirus (COVID-19), in: StatPearls. Treasure Island (FL), StatPearls Publishing, 2020. August 10.
[5]. Centers for Disease Control and Prevention. COVID-NET: COVID-19 associated hospitalization surveillance network. Available at: https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html. Accessed 8 April 2020.
[6]. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; Feb 28.
[7]. Kraemer MU, Yang CH, Gutierrez B, et al.: The effect of human mobility and control measures on the COVID-19 epidemic in China. Science. 2020, 368:493-497.
[8]. Wu Z, McGoogan JM. Characteristics of and important lessons from the corona virus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. J Am Med Assoc 2020.
[9]. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X et al. COVID-19 infection: the perspectives on immune responses.Cell Death Differ 2020.
[10]. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020.
[11]. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science 2020; 368(6490): 473-4.
[12]. Wang F, Nie J, Wang H et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. J Infect Dis 2020.
[13]. T.C. Theoharides, P. Conti, Dexamethasone for COVID-19? Not so fast, J. Biol. Regul. Homeost. Agents 34 (3) (2020 Jun 4) 1–5.
[14]. Isidori AM, Arnaldi G, Boscaro M et al. COVID-19 infection and glucocorticoids: update from the Italian Society of Endocrinology Expert Opinion on steroid replacement in adrenal insufficiency.JEndocrinol Invest April 2020.
[15]. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe 2020; 27:992–1000.e3.
[16]. Villar J, Confalonieri M, Pastores SM, Meduri GU. Rationale for prolonged corticosteroid treatment in the acute respiratory distress syndrome caused by coronavirus disease 2019. Crit Care Explor2020; 2:e0111.
[17]. Y. Wang, W. Jiang, Q. He, et al., A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia, Sig Transduct Target Ther 5 (2020) 57.
[18]. Z. Ye, Y. Wang, L.E. Colunga-Lozano, et al., Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis, CMAJ (Can. Med. Assoc. J.) 192 (27) (2020) E756–E767.
[19]. W. Zhang, Y. Zhao, F. Zhang, et al., The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the Perspectives of clinical immunologists from China, Clin. Immunol. 214 (2020) 108393, https://doi.org/10.1016/j.clim.2020.108393.
[20]. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med 2006;3:e343. https://doi.org/10.1371/journal.pmed.0030343.
[21]. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with middle east respiratory

syndrome. Am J RespirCrit Care Med 2018;197:757.

[22]. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395:473e5. https:// doi.org/10.1016/S0140-6736(20)30317-2.

[23]. Shang L, Zhao J, Hu Y et al. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet 2020;395:683e4. https://doi.org/10.1016/S0140-6736(20)30361-5.

[24]. Chalmers S, Khawaja A, Wieruszewski PM et al. Diagnosis and treatment of acute pulmonary inflammation in critically ill patients: the role of inflammatory biomarkers. World J Crit Care Med. 2019,8:59-71. 10.5492/wjccm.v8.i5.59.

[25]. Zhou W, Liu Y, Tian D, et al. Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia. Signal Transduct Target Ther. 2020, 5:18. 10.1038/s41392-020-0127-9

[26]. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. Available at: https://www.who.int/publications-detail/clinical-management-of-severeacute respiratory-infection-whennovelcoronavirus-(ncov)-infection-issuspected, [Accessed 20 June 2020].

[27]. The Centers for Diseases Control and Prevention, CDC, USA. Covid-19 treatment guidelines. https://files.covid19treatmentguidelines.nih.gov/guidelines/ covid19treatmentguidelines.pdf9. [Accessed 20 June 2020].

[28]. Alhazzani W, Moller M, Arabi YM, Loeb M, Gong MN, Rhodes A, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020;46:854e87.

[29]. T.C. Theoharides, P. Conti, Dexamethasone for COVID-19? Not so fast, J. Biol. Regul. Homeost. Agents 34 (3) (2020 Jun 4) 1–5.

[30]. M.A. Lim, R. Pranata, Worrying situation regarding the use of dexamethasone for COVID-19, Ther. Adv.Respir. Dis. 14 (2020 Jan-Dec).

[31]. T. Rhen, J.A. Cidlowski, Antiinflammatory action of glucocorticoids–new mechanisms for old drugs, N. Engl. J. Med. 353 (16) (2005 Oct 20) 1711–1723.

[32]. V. Selvaraj, K. Dapaah-Afriyie, A. Finn, et al., Short-term dexamethasone in sars- CoV-2 patients, R. I. Med. J. 103 (6) (2020 Jun 19) 39–43.

[33]. R.M. Johnson, J.M. Vinetz, Dexamethasone in the management of covid -19, BMJ 370 (2020 Jul 3) m2648.

[34]. E. Wilkinson, RECOVERY trial: the UK covid-19 study resetting expectations for clinical trials, BMJ (2020) m1626.

[35]. Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARSassociated Coronavirus RNA concentrations in adult patients. J ClinVirol2004; 31(4): 304-9.

[36]. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. Am J RespirCrit Care Med 2018; 197(6): 757-67.

[37]. Lee N, Chan PK, Hui DS, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. J Infect Dis 2009; 200(4): 492-500.

[38]. 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.

[39]. Horby P, Lim WS, Emberson J et al. Effect of dexamethasone in hospitalized patients with COVID-19 e preliminary report. medRxiv June 22,2020..