Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/y4vctc98

METHYLPREDNISOLONE VS. DEXAMETHASONE IN THE TREATMENT OF HYPOXIC COVID-19 PNEUMONIA

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ABSTRACT

BACKGROUND: There has been an on-going debate regarding the choice of the glucocorticoid to be used when treating moderate and severe Corona Viral Disease 2019 (COVID-19) disease. This study attempted to determine the difference in the response to Methylprednisolone vs. Dexamethasone in these patients.

METHODS: This retrospective study aimed to compare the changes produced by Methylprednisolone vs. Dexamethasone on peripheral oxygen saturation (SpO_2) and four serum inflammatory markers namely C-reactive protein (CRP), Ferritin, lactate dehydrogenase (LDH) and D-dimer values after 5 days of administration.

RESULTS: The medical records of 81 patients who received Methylprednisolone and 41 who received Dexamethasone were analysed. It was seen that the improvement in the Methylprednisolone and Dexamethasone groups with respect to their SpO_2, CRP, Ferritin and LDH were both significant after 5 days of therapy. Though the reduction in D-dimer was statistically significant in the Methylprednisolone group, it was not in the Dexamethasone group. The improvement in SpO_2 was higher in those who received Methylprednisolone (7.42 ± 3.49 % vs. 4.88 ± 2.98; p = 0.001) but the changes in the other parameters in both groups were similar.

CONCLUSION: Although both glucocorticoids produce beneficial effects when used in moderate and severe COVID-19 disease, Methylprednisolone may be more effective in improving the hypoxia in comparison to Dexamethasone.

KEY WORDS: Methylprednisolone, Dexamethasone, COVID-19, Hypoxia, Steroids.

INTRODUCTION

The devastating outbreak of Corona viral disease 2019 (COVID-19) has triggered an unprecedented quest for therapeutic agents that could protect against this novel illness. This search has seen several false dawns, premature hype and subsequent disappointments, with several drugs failing short of their initial claimed promise. Many of the well-known pharmacological agents including Azithromycin, Doxycycline, Hydroxychoroquine, antiretroviral drugs, Janus Kinase inhibitors etc were tried for off label use against COVID-19 and so were newer molecules that received emergency use authorization like Remdesivir.[1,2] However the open-label Randomized Evaluation

of Covid-19 Therapy (RECOVERY) trial among hospitalized patients demonstrated that the glucocorticoid dexamethasone provided mortality benefit in moderate and severe COVID-19 disease.[3] This study brought forth the evidence which formed the basis for establishment of the present standard of care in the management of hypoxic COVID-19.[4,5]

The transition from mild to more severe forms of COVID-19 illness is attributed to the so called 'cytokine storm' that occurs with the damage to the endothelium of the pulmonary vasculature. Glucocorticoids (steroids) possess broad spectrum immunosuppressive properties and would be considered as ideal agents to counter this kind of an immune hyper-response. Immune-modulatory effects exerted by them include suppression of pro-inflammatory cytokines like Tumor Necrosis Factor (TNFα) and interleukin 6 (IL6) among several others while they up-regulate the production of annexin 1 which is anti-inflammatory. They also impair the proliferation and functioning of various subtypes of leucocytes.[6] Yet initially the WHO advised against the usage of steroids in patients with COVID-19. This may have been owing to unfavourable past experiences with steroids in other viral pneumonias. Indeed mortality as well as the time taken for viral clearance was shown to be increased when steroids were added in the therapeutic regimen of MERS and influenza.[7]

Dexamethasone and equivalent doses of other steroids such as methylprednisolone have now become a part of the standard of care for patients with COVID-19 pneumonia having hypoxia.[8] Although dexamethasone and methylprednisolone are both synthetic steroids they have certain differences in terms of pharmacokinetics. Dexamethasone is considered to be a more potent glucocorticoid compared to methylprednisolone (1.5 mg of methylprednisolone is equivalent to 8 mg of dexamethasone) and it also has a longer duration of action (36 hours vs. 18 hours). Dexamethasone is also less expensive, more widely available and can be administered as an intravenous bolus dose unlike methylprednisolone that is generally recommended to be administered as a slow infusion, which in times of a COVID-19 crisis can be more convenient from a nursing perspective.[9,10] Nevertheless, there have been suggestions that methylprednisolone is superior to dexamethasone when used in COVID-19 pneumonia. The main reason behind this claim is said to be its better lung penetration.[7] But there are only a limited number of publications at present which have compared methylprednisolone vs. dexamethasone in the treatment of hypoxic COVID-19 illness and even these have described contradictory results. Hence the present study was undertaken to compare the improvement in clinical and biochemical parameters produced by the administration of dexamethasone vs. methylprednisolone in moderate and severe categories of COVID-19 illness.

MATERIALS AND METHODS

Study Design

This was a retrospective study with case record analysis of non-intubated patients admitted to the wards of a designated COVID hospital between July 2020 to November 2020. Ethical clearance was waived off for the study at the institutional review board meeting (MSRMC/EC/AP-05/11-2020) owing to its retrospective design. However strict anonymity was maintained when the data was extracted for analysis.

Inclusion Criteria

- Patients aged 18 years and above diagnosed to have COVID-19 infection after testing positive on reverse transcriptase polymerase chain reaction (RT-PCR) testing for Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-Cov2) performed on nasal and oropharyngeal samples. The RTPCR test was performed on all samples at the National Accreditation Board for Laboratories accredited laboratory attached to the designated COVID hospital. As the first step, the sample was tested for the presence of the open reading frame (ORF) gene, and if this were to be detected then the final step to detect the envelop (E) gene was run. Those who had both ORF and the E genes detected in their samples were deemed to have SARSCov2 infection and were classified as COVID-19 positive.
- Patients with peripheral oxygen saturation (SpO_2) level below 94% measured in the index finger of either upper limb using an Omron CMS50N Contec Pulse Oximeter.

- Patients who had received either parenteral Dexamethasone or Methylprednisolone as part of their treatment protocol for a minimum of 5 days.

Exclusion Criteria

- Patients intubated prior to initiation of steroid therapy
- Confirmed or suspected co-infections with other microbes
- Patients already on long term steroids intake for other indications
- Patients with concurrent heart failure, pulmonary embolism, liver cirrhosis or chronic kidney disease.

The patients' disease severity was categorised according to the following classification
Moderate COVID-19 disease: SpO_2 90-94% on room-air
Severe COVID-19 disease: SpO_2 < 90% on room-air

Ever since the WHO approval for the use of steroids in COVID-19 patients with hypoxia, the treating physicians had been allowed to use their discretion regarding the choice of the steroid. The patients who were treated with dexamethasone received it at an intravenous dose of 8 mg once daily for moderate and twice daily for severe disease while methylprednisolone had been given as an intravenous infusion diluted in 100 ml of normal saline at 40 mg once daily for moderate and twice daily for severe disease. All patients had received anticoagulation as per the standard of care for COVID-19 illness along with a parenteral cephalosporin prophylactic antibiotic coverage.

The details of the patients' demographic details and comorbidities were extracted from the hospital medical records. The laboratory parameters of all patients on the day of initiation (D0) and on the 5^{th} day (D5) of the steroids administration were collected. These included the values of serum C-reactive protein (CRP), Ferritin, lactate dehydrogenase (LDH) and D-dimer values were recorded. Their High resolution computed tomography (HRCT) scan reports were collected and the disease severity was documented. The semiquantitative system was used to grade the extent of lung abnormalities on HRCT based on visual scoring, and scores ranged overall from 0 (no involvement) to 25 (maximum involvement).[11]

Statistical Analysis

Continuous data was represented as mean and standard deviation. Categorical data was represented in the form of frequencies and proportions. Data was entered into Microsoft excel data sheet and Statistical Package for Social Sciences (SPSS) version 20 (IBM SPSS Statistics, Somers New York, USA) was used to analyse the data Chi-square test or Fischer's exact test (for 2x2 tables only) was used as test of significance for qualitative data. Independent t test was used as test of significance to identify the mean difference between two quantitative variables. The p value ≤ 0.05 was taken as significant.

RESULTS

The STROBE flow diagram in figure 1 summarises the methods of consideration of the patients for this study. Eventually the medical case records of 122 COVID-19 patients with hypoxia hospitalised to the wards of the designated COVID hospital were retrieved for analysis. This comprised of 81 patients with who received Methylprednisolone and 41 who received Dexamethasone. The patients in both groups had similar mean age with the majority of them being between 51-60 years. There were significantly higher numbers of male patients in the methylprednisolone group. Though overall there were a higher number of patients in the Methylprednisolone group, the mean HRCT severity score was higher in this group indicating that these patients had a more extensive lung involvement (Table 1). Also there were a higher number of patients with severe category of illness in the methylprednisolone group. This was also reflected in the mean baseline peripheral oxygen saturation in this group which was lower than the dexamethasone group, but this was not statistically significant.

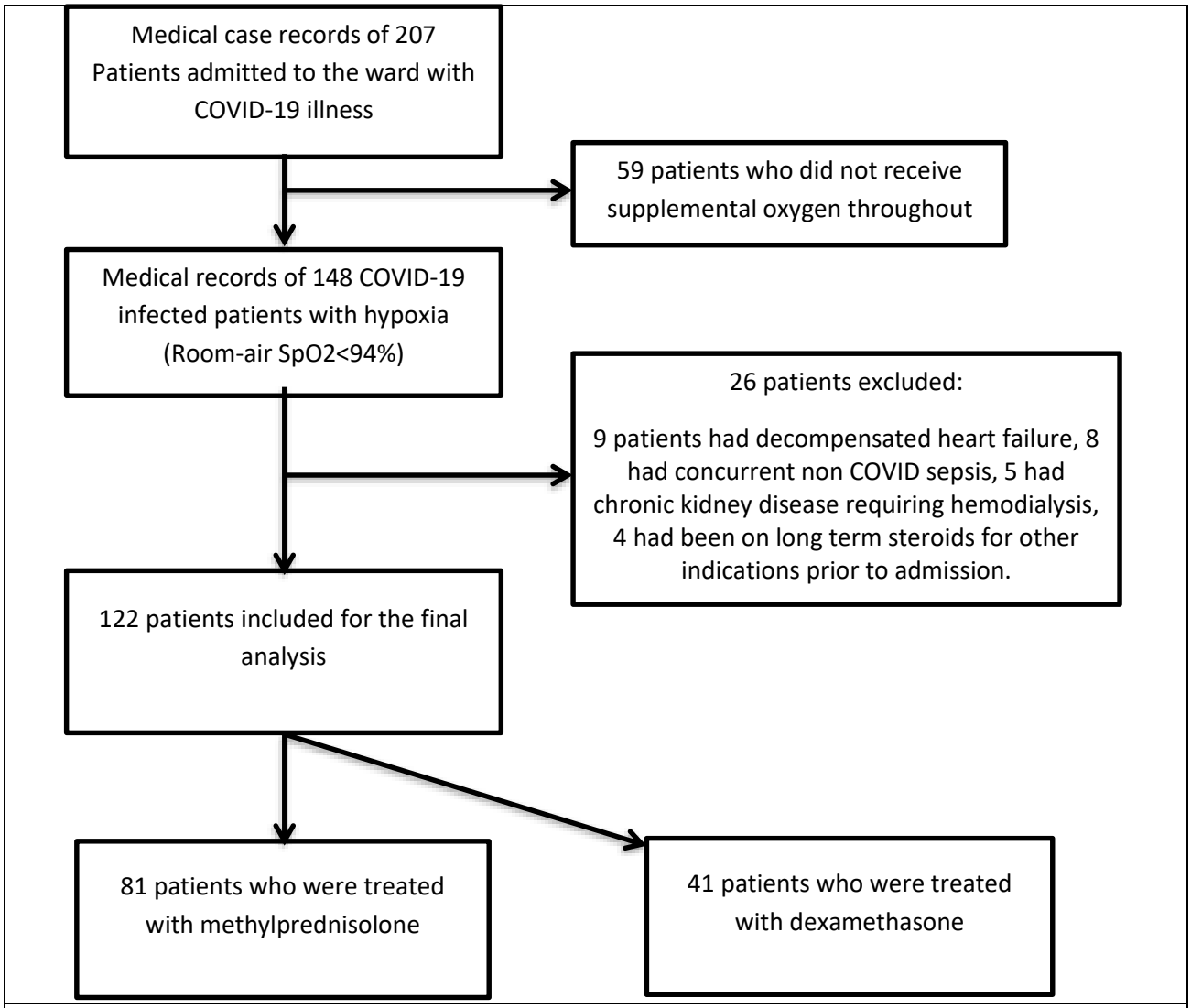

Figure 1. STROBE Flow Diagram

Characteristics		**Methyl Prednisolone n=81**	**Dexamethasone n=41**	**p value**
Age (in years ± Standard deviation)		57.35 ± 15.66	55.85 ± 17.76	0.638
Gender	Female	13	20	0.001
	Male	68	21	
Disease Severity	Moderate	44	34	0.003
	Severe	37	7	
HRCT† severity score ± Standard deviation	(Maximum score 25)	11.74 ± 5.66	8.11 ± 5.08	0.001
Comorbidities	Type 2 Diabetes Mellitus	40	21	0.848
	Hypertension	41	18	0.483
	COPD*	7	3	0.334
	Others	8	4	0.218

Table 1: Baseline Characteristics of the patients

There was significant improvement with regards to the SpO_2, serum CRP, serum LDH and serum ferritin values in both the groups. The the reduction in D dimer level was seen to be statistically significant only in the methylprednisolone group and not in the dexamethasone group. The increase in the SpO_2 levels at D5 from D0 of steroid administration was significantly greater in those who had received methylprednisolone (Table 2).

Study Parameters		Methylprednisolone N=81	Dexamethasone N=41	p-value
Sp02‖ % mean±SD	Day 0†	89.85 ± 3.75	92.74 ± 2.98	0.155
	Day 5‡	97.27 ± 1.25	97.6 ± 1.15	0.150
	Δ Sp02‖	7.42 ± 3.49	4.88 ± 2.98	0.001
	p-value	0.001	0.001	
CRP* mg/dl mean±SD	Day 0†	10.04 ± 7.63	11.25 ± 9.09	0.438
	Day 5‡	3.12 ± 2.88	3.12 ± 2.68	0.993
	Δ CRP	6.92 ± 5.97	8.22 ± 7.11	0.291
	p-value	0.001	0.001	
D-dimer mcg/ml mean±SD	Day 0†	2.32 ± 2.60	10.42 ± 48.34	0.155
	Day 5‡	1.34 ± 1.66	4.29 ± 17.53	0.133
	Δ D-dimer	0.99 ± 2.05	6.24 ± 31.06	0.131
	p-value	0.001	0.207	
Ferritin mcg/dl mean±SD	Day 0†	442.83 ± 283.41	366.25 ± 281.33	0.160
	Day 5‡	242.69 ± 196.51	237.56 ± 241.29	0.900
	Δ Ferritin	200.14 ± 195.67	183.27 ± 199.41	0.656
	p-value	0.001	0.003	
LDH mg/dl mean±SD	Day 0†	434.56 ± 255.57	420.19 ± 218.28	0.759
	Day 5‡	254.19 ± 187.69	206.73 ± 84.82	0.131
	Δ LDH§	180.37 ± 183.56	218.51 ± 217.88	0.331
	p-value	0.001	0.001	

Table 2: Changes in parameters with steroid therapy

DISCUSSION

Only a handful of studies at this moment in time have attempted to compare the role of these two types of steroids in the management of hypoxic COVID-19 disease. This study demonstrated the superiority of methylprednisolone over dexamethasone in ameliorating the hypoxia in patients with moderate and severe COVID19 illness. The patients who received methylprednisolone evidently had a more severe disease at the commencement of therapy as indicated by the lower baseline SpO_2 and higher HRCT severity scores of patients in this group. Despite this, methylprednisolone appeared to be more effective in correcting the hypoxia in these patients. Notably there was a significant improvement observed with respect to the peripheral oxygen saturation and serum markers of disease severity such as CRP, Ferritin and LDH following five days of steroids therapy in both the groups. Yet there was no significant difference in the improvement produced by the two steroids with respect to serum inflammatory markers after five days of steroids therapy. Although the reduction in the levels of D-dimer did not reach statistical significance in the dexamethasone group as opposed to in the methylprednisolone group, this might have been due to the lower sample size.

Randomised controlled trials like the RECOVERY trial as well as the Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19 (CoDEX) have shown beyond doubt that dexamethasone is beneficial in moderate and severe COVID illness.[3,12] The RECOVERY trial, initially with its preliminary results in June 2020 and again with the final results comprehensively demonstrated that the addition of dexamethasone in the treatment of COVID-19 reduced 28 day mortality compared to those on usual care among COVID-19 patients on oxygen support (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) as well as those requiring invasive ventilator support (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81). Similar studies went on to highlight the effectiveness of steroids in COVID-19 illness and hence dexamethasone and equivalent doses of other steroids such as methylprednisolone were incorporated into the standard of care for those with moderate to severe COVID-19 disease. Some authors have proposed that methylprednisolone is more effective than dexamethasone in the treatment of COVID-19 pneumonia presumably owing to its better penetration into the pulmonary parenchyma. Papamanoli et al concluded from their retrospective study among non-intubated COVID-19 patients that a median dose of 160 mg/day of

methylprednisolone was associated with a 37 % reduced probability of ventilator requirement in comparison to patients who did not receive steroids (hazard ratio 0.63; 95% CI 0.47-0.86; p=0.003).[13]

Ranjibar et al conducted a randomized controlled trial in Iran by enrolling 86 patients with varying degrees of severity of COVID-19 illness. The patients were divided into two groups with 2mg/kg/day of methylprednisolone administered in one arm and 6 mg/kg/day of dexamethasone administered in the other arm. This study revealed that methylprednisolone produced a greater reduction in the WHO recommended 9-point ordinal scale for clinical improvement after five and ten days of steroid therapy. They also observed a reduction in the duration of stay as well as ventilator requirement in the methylprednisolone arm, although the overall mortality benefit was not seen to differ significantly compared to dexamethasone.[7]

Justine J. Ko, et al, conducted a retrospective study on COVID-19 patients in the ICU to compare the benefits of methylprednisolone (at 1 mg/kg/day) and dexamethasone (6 mg /kg/day) vs. usual care. Although the outcomes in both steroid groups were seen to be superior to the usual care group, they found that the 104 patients on methylprednisolone had significantly lower all-cause mortality at day 28 and day 50 of the illness in comparison to the 83 patients who received dexamethasone. Yet for patients who were not requiring mechanical ventilation there was no difference between the two steroids in terms of the mortality benefit. The dexamethasone group in the study also had a higher proportion of malignancy and heart failure that may have contributed to the poorer outcomes.[14]
Au contraire, some authors have reported contradictory findings regarding the choice of steroid to be used in COVID-19 illness. A multicentre prospective study carried out in Pakistan compared 65 COVID-19 patients who received methylprednisolone vs. 35 who received dexamethasone. The study failed to find any significant difference between the two types of steroids with respect to the reduction in the supplemental oxygen requirement, ventilator use or serum CRP levels.[15] A retrospective study by Rana MA et al. even demonstrated that 16 mg/day of dexamethasone produced a greater improvement in oxygenation status in comparison to 80 mg/day of methylprednisolone when used in COVID-19 patients requiring bi-level positive airway pressure support. The ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen in the dexamethasone group was greater after 8 days of steroid therapy in comparison to the methylprednisolone group.[16]

Meanwhile some studies have advocated for the use of higher dose of methylprednisolone in COVID-19 disease with hypoxia.[13,17] An ambispective study conducted in Columbia compared 105 patients with severe COVID-19 illness who received 250-500 mg of methylprednisolone for 3 days followed by a course of oral prednisolone vs. 111 patients who were treated with dexamethasone 6 mg/day. The study demonstrated significantly reduced the recovery time, ICU requirement and inflammatory markers such as C-reactive protein (CRP) and D-dimer in these patients.

This study analysed the records of patients who were hospitalised during the first peak of the pandemic in the country. During this time, owing to the unexpected surge in hypoxic patients getting admitted, there was an acute shortage of ICU facilities to accommodate such patients. As a result of these exceptional circumstances, patients with moderate and severe category of COVID-19 illness who should ideally be managed in the ICU settings had to receive treatment in the ward. Hence the authors of this study did not consider comparing the requirement of ICU as an end pint between the two groups. This drawback can be adequately addressed only in randomised control trial settings. The results from the on-going Methylprednisolone vs. Dexamethasone in COVID-19 Pneumonia (MEDEAS RCT ClinicalTrials.gov Identifier: NCT04636671) may provide more definitive answers.

CONCLUSION

Although both methylprednisolone and dexamethasone were seen to produce improvement in room-air peripheral oxygen saturation and serum inflammatory markers in patients with moderate to severe COVID-19 disease, a higher improvement in room-air peripheral oxygen saturation was observed with methyl prednisolone. Hence methylprednisolone should be preferred to dexamethasone in the treatment of patients with COVID-19 infection in the setting of hypoxia. Future large scale prospective studies are warranted to confirm the findings of this study.

Source of Support: None

Conflict of Interest: Nil

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgement: We would like to thank Mr. Balakrishna Gurmitkal for his support in the statistical analysis of the data.

REFERENCES

[1] WHO Solidarity Trial Consortium. Repurposed antiviral drugs for Covid-19 - interim WHO Solidarity Trial Results. N Engl J Med 2021;384(6):497-511.
[2] Butler CC, Dorward J, Yu LM, Gbinigie O, Hayward G, Saville BR, et al. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet 2021;397(10279):1063-74.
[3] The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384(8):693-704.
[4] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.COVID-19treatmentguidelines.nih.gov/.
[5] World Health Organization. Corticosteroids for COVID-19: living guidance, 2 September 2020. World Health Organization 2020. Available at https://apps.who.int/iris/handle/10665/334125.
[6] Annane D. Corticosteroids for COVID-19. Journal of Intensive Medicine 2021;1(1):14-25.
[7] Ranjbar K, Moghadami M, Mirahmadizadeh A, Fallahi MJ, Khaloo V, Shahriarirad R, et al. Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: a triple-blinded randomized controlled trial. BMC Infectious Diseases 2021;21:1-8.
[8] World Health Organization. Therapeutics and COVID-19. Living guideline. 2021. https://www.who.int/publications/i/item/therapeutics-and-covid-19-living-guideline.
[9] Mager DE, Lin SX, Blum RA, Lates CD, Jusko WJ. Dose equivalency evaluation of major corticosteroids: pharmacokinetics and cell trafficking and cortisol dynamics. J Clin Pharmacol 2003;43(11):1216-27.
[10] Tandon R, Verma K, Chawla B, Sharma N, Titiyal JS, Kalaivani M, et al. Intravenous dexamethasone vs methylprednisolone pulse therapy in the treatment of acute endothelial graft rejection. Eye 2009;23(3):635-9.
[11] Ali TF, Tawab MA, ElHariri MA. CT chest of COVID-19 patients: what should a radiologist know? Egypt J Radiol Nucl Med 2020;51:120.
[12] Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: The CoDEX randomized clinical trial. JAMA 2020;324(13):1307-16.

[13] Papamanoli A, Yoo J, Grewal P, Predun W, Hotelling J, Jacob R, et al. High-dose methylprednisolone in nonintubated patients with severe COVID-19 pneumonia. Eur J Clin Investig 2020:e13458.
[14] Ko JJ, Wu C, Mehta N, Wald-Dickler N, Yang W, Qiao R. A Comparison of methylprednisolone and dexamethasone in intensive care patients with COVID-19. J Intensive Care Med 2021;36(6):673-80.
[15] Fatima SA, Asif M, Khan KA, Siddique N, Khan AZ. Comparison of efficacy of dexamethasone and methylprednisolone in moderate to severe COVID-19 disease. Ann Med Surg (Lond) 2020;60:413-6.
[16] Rana MA, Hashmi M, Qayyum A, Pervaiz R, Saleem M, Munir MF, et al. Comparison of efficacy of dexamethasone and methylprednisolone in improving PaO2/FiO2 ratio among COVID-19 patients. Cureus 2020;12(10):e10918.
[17] Pinzón MA, Ortiz S, Holguín H, Betancur JF, Cardona Arango D, Laniado H, et al. Dexamethasone vs methylprednisolone high dose for Covid-19 pneumonia. PLOS One 2021;16(5):e0252057.