Research Article

Steroids use in Severe/ Life Threatening COVID-19 Pneumonia: Does the Type or Dose Matter?

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Abstract

Objective: To compare the effect of different doses of methylprednisolone and dexamethasone on in-hospital mortality in severe COVID-19 pneumonia

Methods: This retrospective chart review was done by reviewing old medical reports of patients with severe disease admitted to COVID-19 Intensive Care and High Dependency Unit from October 2020 to September 2021. Those with suspected COVID-19 infection (suggestive radiological findings but negative PCR for SARS-CoV- 2 on at least two occasions) were excluded. Patients requiring high flow oxygen (>6 liters per minute) or higher levels of respiratory support were classified as having severe disease. We recorded the type of steroids used and the doses. Methylprednisolone in doses up to 40mg per day, or other steroids in equivalent doses, were considered low dose. Primary outcome of interest was in- hospital mortality.

Results: There were 279 patients aged 52.53± 11.31 years, including 216 (77.42%) males. Mean hospital stay was 10.18± 3.13 days. During hospital stay, 96 (34.41%) patients died. Amongst patients receiving dexamethasone, 70 (44.87%) expired, whereas 26 (21.14%) out of 123 patients who received methylprednisolone expired ($p<0.001$; hazard ratio 3.037). With high dose steroids, 52 (41.27%) out of 126 patients expired, whereas 44 (28.76%) out of 153 patients treated with low dose steroids expired ($p=0.029$; hazard ratio 1.741). In multivariate binary logistic regression, in-hospital mortality was related to the type of steroid but not the steroid dose.

Conclusion: Methylprednisolone is superior to dexamethasone for treatment of severe COVID-19 pneumonia.

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Introduction:

Pakistan is currently under the grip of the fifth wave of COVID-19 infection. Whereas most of the patients are asymptomatic or have mild disease only, a significant proportion of them are at an increased risk of complications, need for invasive mechanical ventilation or even death.[1] Despite almost two years since the onset of this pandemic, the ideal treatment strategy is still not clearly defined.[2] Many therapeutic options have been tested, all revolving around either the virus itself or the cytokine storm that it induces. Whereas some of them, such as convalescent plasma, faded out with time and others, such as oral antivirals, continue to evolve, steroids still enjoy a central place in the armamentarium against this deadly disease.[3-5] Though the RECOVERY trial has provided an insight into ideal therapeutic dose of dexamethasone that could prevent adverse outcomes in hospitalized patients, different types of steroids are still being used in varying doses in various healthcare settings.[6] Despite growing evidence in favour of these drugs, there is still no uniformly acceptable steroid regi-

men in COVID-19 pneumonia. Differences in response to steroids based on ethnicity of patients have been documented previously in other diseases, such as renal allograft rejection.[7] Whereas COVID-19 infection is relatively new and the experience in management not extremely extensive, we could extrapolate previously available evidence to think that the results of response to steroids from western countries might not be generalizable to our patients because of the said reasons. We therefore carried out a retrospective chart review at our hospital from October to November 2021 to assess usage of steroids amongst patients with severe/ life threatening COVID-19 infection and their effects on in-hospital mortality, so as to learn from our own experience. The results would help us adjust our local policies regarding use of steroids accordingly.

Methods

This retrospective chart review study was carried out at Combined Military Hospital Peshawar from October 2020 to November 2021. Approval from Ethics Review Committee of the hospital was obtained vide reference number 329/21 dated 12 Sep 2021 before start of the study. Sample size calculation was done using the online Epitools Sample Size Calculator to detect a significant difference between two proportions. Based on assumptions that the all-cause mortality would be 35.71% in dexamethasone group and 18.18% in methylprednisolone group as documented by Ranjbar, et al, there was a requirement for a minimum of 222 patients to be included in this study.[8] For this calculation, we also assumed 95% confidence interval, 80% power and used a two tailed test. Non probability consecutive sampling technique was used. We retrieved paper medical reports of patients with severe/ life threatening disease admitted to COVID-19 Intensive Care and High Dependency Units of the hospital from October 2020 to September 2021. Relevant information for these cases was also obtained from records of Radiology Department as well as the Hospital Laboratory Management System software. Patients identity was kept anonymous and no informed consent was taken from their next of kins. Patients with suspected COVID-19 infection (suggestive radiological findings but negative PCR for SARS- CoV-2 on at least two occasions) or having incomplete data were excluded. For this study, patients requiring high flow oxygen (>6 liters per minute) or higher levels of respiratory support were classified as having severe disease. Basic demographic data of the study participants was noted down. We also recorded duration of symptoms, hospital stay and use of other therapies including remdesivir, tocilizumab and plasma exchange. The type of steroids used and their doses were documented. Methylprednisolone in doses up to 40mg per day, or other steroids in equivalent doses, were considered low dose. The primary outcome of interest was in- hospital mortality.

Data were analyzed with IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp, Armonk, NY). Chi square test was used to determine the relationship of different steroid types and doses with mortality. Multivariate binary logistic regression was done to see if in-hospital mortality is affected by the different types of steroids or their use in different doses. For all these tests, $p < 0.05$ was considered statistically significant.

Results

There were 279 patients having a mean age of 52.53± 11.31 years. These included 216 (77.42%) males and 63(22.58%) females. Duration of symptoms at the time of admission was 13.90±4.12 days and the mean hospital stay was 10.18±3.13 days. During stay in the hospital, 96(34.41%) patients died. Number of patients receiving different steroids in variable doses is shown in Table 1. The use of other specific therapies in different groups of patients is shown in Table 2. As far as the different formulations of steroids are concerned, 70(44.87%) out of 156 patients who received dexamethasone expired, whereas 26(21.14%) out of 123 patients who received methylprednisolone expired. This difference was statistically significant ($p<0.001$). Hazard ratio for mortality in patients treated with dexamethasone was 3.037 (95% CI 1.777, 5.188). Kaplan- Meier curve for survival amongst patients with different types of steroids is shown in Figure 1. With regards to the different doses of steroids used in this study, 52 (41.27%) out of 126 patients treated with high dose steroids expired, whereas 44(28.76%) out of 153 patients treated with low dose steroids expired. This difference was statistically significant ($p=0.029$). Hazard ratio for mortality in patients treated with high dose steroids was 1.741 (95% CI 1.058, 2.865). Since the use of plasma exchange was more frequent in patients treated with dexamethasone, it was

also included in multivariate binary logistic regression. As is evident from the statistics in Table 3, in-hospital mortality was related to the use of dexamethasone but not the steroid dose or use of plasma exchange.

Table 1: *Use of Steroids Amongst Patients with Severe/ Life Threatening COVID-19 Infection*

	Dexa-methasone	Methyl-prednisolone	Total
Low dose	70	83	153
High dose	86	40	126
Total	156	123	279

Table 2: *Use of Other Therapies in Different Groups*

		Methylprednisolone	Dexamethasone	*p*	High dose steroids	Low dose steroids	*p*
Tocilizumab	Yes	19 (15.45%)	23 (14.74%)	0.870	21 (16.67%)	21 (13.73%)	0.494
	No	104 (84.55%)	133 (82.26%)		105 (83.33%)	132 (86.27%)	
Remdesivir	Yes	91 (73.98%)	110 (70.51%)	0.521	86 (68.25%)	115 (75.16%)	0.201
	No	32 (26.02%)	46 (29.49%)		40 (31.5%)	38 (24.84%)	
Plasma exchange	Yes	20 (16.26%)	44 (28.21%)	0.018	32 (25.40%)	32 (20.92%)	0.376
	No	103 (83.74%)	112 (71.79%)		94 (74.60%)	121 (79.08%)	

Table 3: *Results of Multivariate Binary Logistic Tegression*

Variable	Exp(B)	95% CI for Exp(B)	*p*
Dose of steroids*	1.410	0.837, 2.376	0.196
Type of steroid^	2.740	1.580, 4.752	<0.001
Plasma exchange~	1.310	0.722, 2.378	0.374

Reference category *Low dose, ^Methylprednisolone, ~no

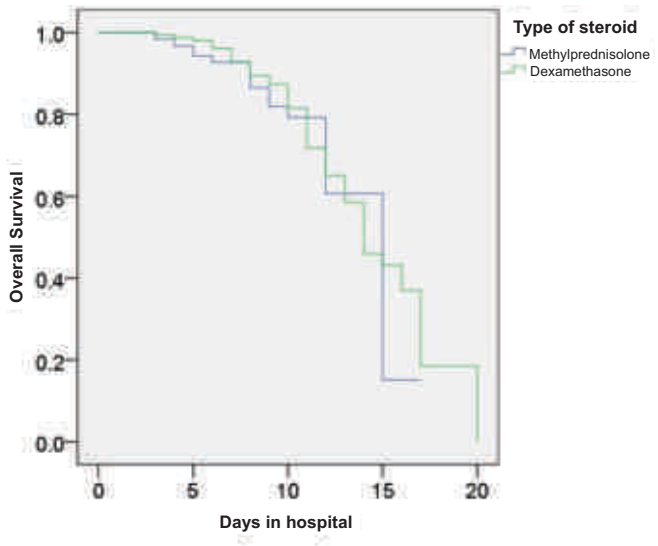

Figure 1: *Kaplan-Meier Survival Curve*

Discussion

Corticosteroids have been used as immune modulator agents in a wide variety of diseases since long. COVID-19 infection is characterized by activation of inflammatory cascade and multiorgan dysfunction resulting from injury to alveolar epithelial cells by SARS-CoV-2. Anti-inflammatory effects of corticosteroids result from the stimulation of synthesis and release of anti-inflammatory proteins and by inhibition of pro-inflammatory cytokines.[9] It is thus not surprising that steroids play a cardinal role in management of COVID-19 pneumonia.

Our results have proven the superiority of methylprednisolone over dexamethasone in severe disease. Better penetration of methylprednisolone into lungs as compared to dexamethasone, with better drug levels at tissue level, might be the reason for this.[10] Available evidence in this regard gives variable results. A quasi-experimental study with 100 participants done at Lahore concluded that both these types of steroids are equally effective.[11] A systematic review and meta-analysis of three studies involving 373 patients also showed no difference between the two steroids, though the grade of evidence for this was very low.[12] On the contrary, in a retrospective review of 513 patients from Morocco, survival was better amongst patients treated with dexamethasone (almost 8% better), though the authors have not mentioned the statistical significance of this difference.[13] Amongst 242 patients, Du Plessis et al showed shortened duration of hospital stay with high dose methylprednisolone, but no difference in mortality when compared to low dose dexamethasone.[14]

A major strength of our study deign is that we stratified patients into treatment groups based on equivalent steroid doses and excluded the effect of steroid dose by multivariate logistic regression analysis. To the best of our knowledge, comparison of steroid treatment for severe COVID-19 pneumonia in same doses has not been reported on Pubmed or Google Scholar before.

When seen as part of the bigger overall picture, the dose of steroids was not related to poor outcomes (insignificant adjusted Odds ratio). Monreal, et al have presented opposite results.[15] Amongst 573 Italian patients, there was a greater risk of mortality with high dose steroids, an effect was more marked in the elderly patients. Another local study by Jamil et al also found low dose dexamethasone to be more useful in preventing outcomes when compared to much higher doses of methylprednisolone.[16]

Most of the literature revolves around studies using higher doses of methylprednisolone than equivalent doses of dexamethasone. In a randomized controlled trial on 86 patients from Iran, methylprednisolone was superior to dexamethasone, though the authors are not clear whether this was due to the drug or the higher dose.[17] Similarly, another trial from Colombia reported better outcomes with much higher doses of methylprednisolone.[18]

More patients receiving methylprednisolone had plasma exchange done, as compared to those getting dexamethasone. The impact of this factor on mortality was catered for by including plasma exchange in multivariate logistic analysis. Other than tis, there was no difference in use of novel therapies amongst groups based on steroid doses or types. Another important finding from this study was a much lower mortality rate than the 90.91% reported in an earlier study from our hospital.[19] This is simple a reflection of greater experience in managing such cases.

It is important to understand some limitations of this study, so that the results may be interpreted accordingly. Clinical research requires meticulous planning and execution by a dedicated team of healthcare professionals. The system is already overburdened in Pakistan, and resources are quite limited. Effective delivery of healthcare became more challenging during COVID-19 pandemic, making research even more difficult. For this reason, we chose retrospective review design for this study. Considering the retrospective design, we could not cater for other factors known to be related to mortality, such as co-morbid conditions, levels of inflammatory markers or complications including acute kidney injury. Randomization into treatment groups at the time of admission might have given us somewhat different results. The need for mechanical ventilation was not compared amongst the different groups and the patients were not followed up after discharge, so we are not confident about the superiority of methylprednisolone being maintained in the following few weeks. Moreover, no side effects to treatment were recorded, and thus its impact on morbidity in our patients could not be gauged. We would suggest prospective multi-center randomized clinical trials with coordination at regional and national level for affirmation of our results.

Conclusion

The use of dexamethasone in our patients with severe COVID-19 pneumonia is associated with higher mortality. Methylprednisolone is thus recommended as the steroid of choice under such circumstances. The dose should be directed by the specific clinical circumstances, with due consideration given to the potential side effects.

Authors' contribution: ARA: Data analysis, study design, critical revision, final approval, fully accountable; **BS:** Collected data, Study design, drafted manuscript, final approval, fully accountable; **SH:** Collected Data, drafted manuscript, final approval, fully accountable.

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References:

1. UlHaq Z, Shahzad M, Khattak MI, Fazid S, Ullah N, Shireen A, et al. Clinical characteristics, mortality and associated risk factors in COVID-19 patients reported in ten major hospitals of Khyber Pakhtunkhwa, Pakistan. J Ayub Med Coll Abbottabad .2020; 32(Suppl 1)(4): S633-S639.
2. Spicer AJ, Jalkanen S. Why haven't we found an effective treatment for COVID-19? Front Immunol. 2021; 12: 644850.
3. Estcourt L, Callum J. Convalescent plasma for Covid-19 - making sense of the inconsistencies. N Engl J Med. 2022; 386(18):1753-1754.
4. World Health Organization. WHO recommends against the use of convalescent plasma to treat COVID-19 [Internet]. 2023 [updated 2021 December 7; cited 2023 Jan 23]. Available from: https://www.who.int/news/item/07-12-2021-who-recommends-against-the-use-of-convalescent-plasma-to-treat-covid-19
5. Burdet C, Ader F. Real-world effectiveness of oral anti-

virals for COVID-19. Lancet .2022; 400(10359): 1175-1176.

6. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021; 384(8):693-704.
7. Vasquez EM, Benedetti E, Pollak R. Ethnic differences in clinical response to corticosteroid treatment of acute renal allograft rejection. Transplantation. 2001; 71(2): 229-33.
8. 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 Infect Dis. 2021; 21(1):337.
9. Annane D. Corticosteroids for COVID-19. J Intensive Med .2021; 1(1): 14-25.
10. Annane D, Pastores SM, Arlt W, Balk RA, Beishuizen A, Briegel J, et al. Critical illness-related corticosteroid insufficiency (CIRCI): a narrative review from a Multi-specialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). Intensive Care Med. 2017; 43(12):1781–92.
11. Fatima SA, Asif M, Khan KA, Siddique N, Khan AZ. Comparison of efficacy of dexamethasone and methyl-prednisolone in moderate to severe covid 19 disease. Ann Med Surg (Lond) . 2020; 60:413-416.
12. Mohanty RR, Das S, Padhy BM, Meher BR. Comparison of clinical outcome between dexamethasone and methyl prednisolone in treatment of moderate to severe COVID-19: A systematic review and meta-analysis. J Assoc Physicians India . 2022; 70(1):11-12.
13. El Mezzeoui S, El Aidouni G, Merbouh M, El Kaouini A, Aftiss FZ, Berrichi S, et al. Dexamethasone or methyl-prednisolone therapy in covid-19 pneumonia: A retrospective and comparative study of 513 cases. Ann Med Surg (Lond) .2021; 70:102858.
14. Du Plessis EM, Lalla U, Allwood BW, Louw EH, Nortje A, Parker A, et al. Corticosteroids in critical COVID-19: Are all corticosteroids equal? S Afr Med J. 2021; 111(6):550-553.
15. Monreal E, Sainz de la Maza S, Natera-Villalba E, Beltrán-Corbellini Á, Rodríguez-Jorge F, Fernández-Velasco JI et al. COVID-HRC group. High versus standard doses of corticosteroids in severe COVID-19: a retrospective cohort study. Eur J Clin Microbiol Infect Dis. 2021; 40(4):761-769.
16. Jamil Z, Almajhdi FN, Khalid S, Asghar M, Ahmed J, Waheed Y. Comparison of low-versus high-dose steroids in the clinical outcome of hospitalized COVID-19 patients. Antibiotics (Basel) . 2021; 10(12):1510.
17. 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 Infect Dis. 2021; 21(1):337.
18. Pinzón MA, Ortiz S, Holguín H, Betancur JF, Cardona Arango D, Laniado H, et al. Dexamethasone vs methyl-prednisolone high dose for Covid-19 pneumonia. PloS One .2021; 16(5):e0252057.
19. Arshad AR, Khan I, Shahzad K, Arshad M, Haider SJ, Aslam MJ. Association of inflammatory markers with mortality in COVID-19 infection. J Coll Physicians Surg Pak .2020; 30(10):158-163.