



Early View

Editorial

Are intravenous corticosteroid pulses superior to low dose corticosteroids in patients with severe Covid-19?

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Are intravenous corticosteroid pulses superior to low dose corticosteroids in patients with severe Covid-19?

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Corticosteroids were the first drugs proven to reduce mortality in Covid-19. In June 2020, the RECOVERY group announced the results of their seminal trial showing dexamethasone 6mg per day was able to reduce 28-day mortality in hospitalized patients with Covid needing supplemental oxygen or mechanical ventilation (1). Meta-analysis from randomized controlled trials (RCT) in Covid-19 patients confirmed RECOVERY results (2). In those RCTs, corticosteroid doses were low (dexamethasone 6mg per day) or intermediate (dexamethasone up to 20mg per day).

Early in the Covid-19 pandemics, some authors proposed that severe cases of Covid-19 evolved with a cytokine storm with characteristics resembling the hemophagocytic lymphohistiocytosis, an hyperinflammatory syndrome characterized by a fulminant and often fatal hypercytokinemia with multiple organ dysfunction(3). The cytokine storm hypothesis has led many to propose, and prescribe, high dose corticosteroids for severe or critical Covid-19 patients.

Several observational studies assessing corticosteroid pulse versus low-dose corticosteroids for patients with Covid-19 have been reported, many with favorable results on clinical outcomes (4-14). Main characteristics and results of these studies are available in Table 1. A systematic review with meta-analysis of those studies showed a non-statistically significant effect on mortality (odds ratio, 0.66; 95% confidence interval, 0.44 to 1.01; P=0.05) (15). However, confounding bias can hardly be discarded as an explanation for apparent treatment effects obtained in observational studies. One trial of methylprednisolone pulse (250mg/day for three days) for Covid-19 patients was reported in the *European Respiratory Journal*, although the control group of that study did not receive any corticosteroid therapy (9). Therefore, robust evidence from randomized controlled trials to address the question of whether pulse

corticosteroids are superior to low dose corticosteroids for patients with severe Covid-19 was needed.

In this issue of the *European Respiratory Journal*, Salvarani and colleagues report a double-blind, randomized controlled trial comparing intravenous methylprednisolone pulses (1g per day) for 3 consecutive days or placebo in addition to standard dexamethasone in hospitalized patients with COVID-19 (16). The authors conducted a rigorous study, the first randomized controlled trial aiming to respond a very relevant questions many clinicians posed themselves while caring for patients with severe Covid-19.

The trial included hospitalized patients with confirmed Covid-19 pneumonia with more than 5 days initial symptoms, requiring supplemental oxygen (except mechanical ventilation), with PaO₂/FiO₂ between 100-300, and C-reactive protein greater than 5mg/dL. Patients in both groups received standard treatment dexamethasone (6 mg/day oral or intravenous for 10 days). The primary outcome was the duration of the hospitalization (the time interval between randomization and hospital discharge without supplemental oxygen).

A total of 304 patients were enrolled (152 randomized to methylprednisolone group and 152 to placebo). 112 (75.4%) patients in the pulse group and 111 (75.2%) in the placebo group were discharged without oxygen within 30 days (hazard ratio 0.92, 95% CI, 0,71 to 1.20). No difference was observed in time to discharge (15 vs 16 days, respectively). No benefits were showed in the secondary outcomes for the methylprednisolone vs placebo group: admission to ICU or death (20.0% vs 16.1%); deaths (10.0% vs 12.2%); or on other exploratory analyses. Adverse events were reported in 34.2% of participants in the placebo group, and 36.2% in the methylprednisolone group.

Why was the pulse methylprednisolone pulse therapy not superior to the 6mg per day dexamethasone therapy? The cytokine storm was proposed early in the Covid-19 pandemics, however a subsequent rapid systematic review questioned the role of cytokine storm in patients with Covid-19. Compared to patients with severe or critical Covid-19, levels of interleukin-6 were nearly 100 times higher in patients with chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome, 27 times higher in patients with sepsis of other causes, and 12 times higher is patients with acute respiratory syndrome unrelated to Covid-19 (17). Thus, a possible explanation for lack of benefit of pulse corticosteroids is that excessive immunosuppression is unnecessary for most patients with severe or critical Covid-19.

One might also wonder that methylprednisolone pulses might be beneficial for critical cases needing invasive mechanical ventilation or for subsets of patients evolving with severe

progressive ARDS after many days of mechanical ventilation. These subsets of patients were not enrolled in the trial. Heterogeneity of treatment effects according to degrees of inflammatory response was not assessed, and would be valuable in future trials comparing different corticosteroid doses for Covid-19.

A third possible explanation for lack of significant effect of methylprednisolone pulse on the clinical outcome is insufficient sample size. The trial effect estimate on time to discharge without oxygen was imprecise. The 95% confidence interval around the hazard ratio is compatible with both a substantial benefit (95% CI lower limit, 0.71) or harm (95% upper limit, 1.20). Therefore, although the results do not suggest an effect on the primary outcome, they also do not rule it out.

Highly reliable evidence supports use of oral or intravenous corticosteroids at low doses (e.g. dexamethasone 6mg per day) for hospitalized patients with Covid-19 needing supplemental oxygen or mechanical ventilation. However, the results from available studies are inconclusive regarding the effect of intravenous corticosteroid pulses as compared to low dose corticosteroids in Covid-19. Hence, corticosteroid pulses should not be generally used in clinical practice outside the context of clinical trials.

Table 1. Studies comparing intravenous corticosteroid pulses versus low dose corticosteroids or no corticosteroids for hospitalized Covid-19 patients

Study	Design	Country	Patients	Intervention	Comparison	Main results
Batirel 2021 ⁽⁸⁾	Retrospective cohort	Turkya	N=450 Mild to severe	Methylprednisolone 250mg/day	Dexamethasone 6mg/day No corticosteroid	Length of ICU stay: 4.5 on pulse steroids, 8 days on dexamethasone, 9 days on standard care.
Fernandez-Cruz 2020 ⁽¹⁰⁾	Retrospective cohort	Spain	N=463 Moderate to severe	Methylprednisolone >125mg/day	Methylprednisolone 1mg/kg/day	Mortality pulse group 15.1% vs 13.5% low dose (P=0.71)
Dafni 2022 ⁽⁴⁾	Retrospective cohort	Greece	N=58 Severe to critical	Methylprednisolone 250mg/day	Dexamethasone 6mg/day	Duration of hospitalization was shorter for those who received methylprednisolone pulses (9.5 vs 13.5, p<0.001).
Edalatifard 2020 ⁽⁹⁾	Randomized controlled trial	Iran	N=68 Severe	Methylprednisolone 250mg/day for 3 days	No corticosteroid	Clinical improvement (94.1% vs 57.1%) and mortality (5,9% vs 42,9%) better with pulse methylprednisolone
Ruiz-Irastorza 2020 ⁽⁸⁾	Retrospective cohort	Spain	N=242 Moderate to severe on second week	Methylprednisolone 125mg to 250mg/day	No corticosteroid	Adjusted hazard ratio for death 0.35 (95% CI, 0.11 to 1.06) and HR for death or intubation 0.33 (95% CI, 0.13 to 0.84)
Liu 2020 ⁽¹²⁾	Prospective cohort	China	N= 31 Mild to critical	Methylprednisolone >2mg/kg/day	Methylprednisolone ≤2mg/kg/day	No difference in T-lymphocyte count or IL6 levels
Mareev 2020 ⁽¹³⁾	Retrospective cohort	Russia	N=34 Severe	Methylprednisolone 1,000mg/day	No corticosteroid	Improvement in clinical status and inflammatory markers with corticosteroids
Pinzon 2021 ⁽¹⁴⁾	Retrospective and prospective cohort	Colombia	N=216 Severe	Methylprednisolone 250mg to 500mg/day for 3 days	Dexamethasone 6mg/day	After starting the corticosteroid, transfer to the intensive care unit (4.8% vs. 14.4%) and mortality (9,5% vs. 17.1%) was lower in the group that received methylprednisolone.
Rodriguez-Baño 2020 ⁽¹¹⁾	Retrospective cohort	Spain	N=195 Moderate to severe	Methylprednisolone equivalent >250mg/day	Methylprednisolone equivalent ≤125mg/day	Intubation or death up to 21 days in 27/117(23.1%) intermediate to high dose vs 12/78 (15.4%) in pulse group
Lopez Zuniga 2020 ⁽⁵⁾	Prospective cohort	Spain	N=318 Moderate to severe	Methylprednisolone ≥1.5mg/kg/day (or dexamethasone equivalent dose)	Methylprednisolone <1.5mg/kg/day (or dexamethasone equivalent dose)	Reduction in mortality (HR, 0.09; 95% CI, 0.02 to 0.36)

Abbreviations: ICU, intensive care unit; HR, hazard ratio; CI, confidence interval.

References

1. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19 [press release]. University of Oxford 2020.
2. Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *Jama*. 2020.
3. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-4.
4. Dafni M, Karampeli M, Michelakis I, Manta A, Spanoudaki A, Mantzos D, et al. Treatment with 3-day methylprednisolone pulses in severe cases of COVID-19 compared with the standard regimen protocol of dexamethasone. *J Investig Med*. 2022.
5. López Zúñiga M, Moreno-Moral A, Ocaña-Granados A, Padilla-Moreno FA, Castillo-Fernández AM, Guillamón-Fernández D, et al. High-dose corticosteroid pulse therapy increases the survival rate in COVID-19 patients at risk of hyper-inflammatory response. *PLoS One*. 2021;16(1):e0243964.
6. Ruiz-Irastorza G, Pijoan JI, Bereciartua E, Dunder S, Dominguez J, Garcia-Escudero P, et al. Second week methyl-prednisolone pulses improve prognosis in patients with severe coronavirus disease 2019 pneumonia: An observational comparative study using routine care data. *PLoS One*. 2020;15(9):e0239401.
7. Toda M, Fujii K, Yoshifuji A, Kondo Y, Itoh K, Sekine K, et al. Clinical efficacy and safety of combination therapy of tocilizumab and steroid pulse therapy for critical COVID-19 in HD patients. *Clin Exp Nephrol*. 2022;26(1):75-85.
8. Batirel A, Demirhan R, Eser N, Korlu E, Tezcan ME. Pulse steroid treatment for hospitalized adults with COVID-19. *Turk J Med Sci*. 2021;51(5):2248-55.
9. Edalatfard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S, et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. *Eur Respir J*. 2020;56(6).
10. Fernandez-Cruz A, Ruiz-Antoran B, Munoz-Gomez A, Sancho-Lopez A, Mills-Sanchez P, Centeno-Soto GA, et al. A Retrospective Controlled Cohort Study of the Impact of Glucocorticoid Treatment in SARS-CoV-2 Infection Mortality. *Antimicrob Agents Chemother*. 2020;64(9).
11. Rodriguez-Bano J, Pachon J, Carratala J, Ryan P, Jarrin I, Yllescas M, et al. Treatment with tocilizumab or corticosteroids for COVID-19 patients with hyperinflammatory state: a multicentre cohort study (SAM-COVID-19). *Clin Microbiol Infect*. 2021;27(2):244-52.
12. Liu F, Ji C, Luo J, Wu W, Zhang J, Zhong Z, et al. Clinical characteristics and corticosteroids application of different clinical types in patients with corona virus disease 2019. *Sci Rep*. 2020;10(1):13689.
13. Mareev VY, Orlova YA, Pavlikova EP, Matskeplishvili ST, Krasnova TN, Malahov PS, et al. [Steroid pulse -therapy in patients With coronAvirus Pneumonia (COVID-19), sYstemic inFLammation And Risk of vEnous thRombosis and thromboembolism (WAYFARER Study)]. *Kardiologiya*. 2020;60(6):15-29.
14. Pinzon MA, Ortiz S, Holguin 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.
15. Mohanty RR, Biswa Mohan P, Meher BR. Effectiveness of pulse dose methyl prednisolone in management of COVID 19: A systematic review and meta-analysis of observational studies. *J Pharm Pharm Sci*. 2022;25:110-23.
16. Salvarani C, Massari M, Constantini M, Merlo D, Mariani G, Viali P, et al. Intravenous methylprednisolone pulses in hospitalized patients with severe Covid-19 pneumonia, A double-blind, randomized, placebo-controlled trial. *Eur Respir J*. 2022.

17. Leisman DE, Ronner L, Pinotti R, Taylor MD, Sinha P, Calfee CS, et al. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. *Lancet Respir Med*. 2020;8(12):1233-44.