Clinical Infectious Diseases

CORRESPONDENCE

Corticosteroids in Patients With COVID-19: What About the Control Group?

To the Editor—The effect of corticosteroids in coronavirus disease 2019 (COVID-19) still needs to be examined [1–3]. In their recent article in this journal, Fadel et al [4] compared 2 groups of patients hospitalized with COVID-19, with more than half of them receiving corticotherapy in both groups (68.2% vs 56.8%; $P = .094$), but different median (interquartile range) time between hospitalization and therapy initiation (2 [1–3] days, vs 5 [IQR, 3–7] days). Negative evolution of the disease occurred less often in the early group (34.9 vs 54.3%; $P = .005$). They conclude that corticotherapy may improve the evolution of COVID-19 [4]. To reach this conclusion, comparison of treated and untreated patients should have been made.

In our hospital, we investigated retrospectively all cases of confirmed COVID-19 requiring >3 L of oxygen, in adult patients hospitalized between 10 March and 9 April 2020. The outcome of interest was orotracheal intubation, and we aimed to study the effect of corticotherapy. The study received approval from our ethics committee, the patients were informed, and the study was declared to the National Comity for Informatics and Liberties. The independent contribution of the patient's characteristics to the risk of intubation was analyzed by logistic regression (Table 1). To compute the average treatment effect (ATE) of corticotherapy on intubation, we calculated a propensity score (PS) of exposure to corticosteroids using a logistic regression model, including age, sex, Charlson index >1, body mass index >25 kg/m^2, hypertension, time from initiation of symptoms to hospitalization >7 days, C-reactive protein >150 mg/L, oxygen >3 L, treatment with hydroxychloroquine, and azithromycin. These variables include potential confounders (related to treatment and outcome) and prognosis of the outcome [5]. We used PS matching, matching 1:1 to the nearest neighbor with a caliper of 0.25, to estimate the ATE on intubation of a treatment in a population where all individuals have the same probability of receiving the treatment. As sensitivity analysis, we used inverse probability weighting with the PS.

Of 70 cases, 35 (50%) required mechanical ventilation, due to respiratory failure (Supplementary Table 1). Corticotherapy affected the risk of intubation with a risk difference (ATE) of −47.1% (95% confidence interval [CI], −71.8 to −22.5). Using inverse probability weighting, the ATE was similar: −47.5% (95% CI, −70.0% to −25.0%). Among the 49 patients who did not receive corticosteroids, 32 (65%) were intubated. Based on these results, systematic corticotherapy may have resulted in 65% − 47.1% = 17.9% (ie, 12 intubations overall). That would have lifted the pressure on the limited number of beds at the intensive care unit.

Fadel et al found that the effect of corticosteroid varies according to the timing of their administration. In our study, mean duration of symptoms before hospitalization was 7.6 ± 4 days, and mean duration before corticosteroid initiation was 13.0 ± 4.2 days. In our opinion, it is the delay after symptom onset that presents a practical interest. This information is rarely found in other comparative studies [4, 6–9].

Further studies are urgently needed, to determine not only the effect and the best timing of corticosteroids in COVID-19, but also the best protocol of administration in the best target population.

Table 1. Multivariable Odds Ratios of Intubation Associated With Patient Characteristics (N = 70)

Characteristic	Odds Ratio (95% CI)	*P* Value
Age	1.12 (.98–1.29)	.105
Sex	0.18 (.01–4.71)	.303
Charlson index >1	9.52 (.55–164.42)	.121
BMI ≥25 kg/m^2	1.34 (.06–29.28)	.852
High blood pressure	4.18 (.44–39.81)	.213
Duration before hospitalization >7 d	0.36 (.032–4.17)	.416
Oxygen dose at entrance >3 L/min	54.69 (2–1497.49)	.018
Highest CRP >150 mg/L	73.47 (2.37–2277.84)	.014
Azithromycin	0.36 (.02–5.19)	.451
Hydroxychloroquine	99.36 (1.67–5907.55)	.027
Corticosteroids	< 0.001 (3.24 x 10^{-06} to .09)	.004

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet **2020**; 395:473–5.
2. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet **2020**; 395:1033–4.
3. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19 [manuscript published online ahead of print 27 April 2020]. Clin Infect Dis **2020**. doi:10.1093/cid/ciaa478.
4. Fadel R, Morrison Austin R, Vahia A, et al. Early short course corticosteroids in hospitalized patients with COVID-19 [manuscript published online ahead of print 19 May 2020]. Clin Infect Dis **2020**. doi:10.1093/cid/ciaa601.
5. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T. Variable selection for propensity score models. Am J Epidemiol **2006**; 163:1149–56.
6. Zha L, Li S, Pan L, et al. Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19). Med J Aust **2020**; 212:416–20.
7. Wang Y, Jiang W, He Q, et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. medRxiv [Preprint]. Posted 12 March **2020**. doi:10.1101/2020.03.06.20032342
8. Wang Y, Jiang W, He Q, et al. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia. Signal Transduct Target Ther **2020**; 5:57.
9. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China [manuscript published online ahead of print 13 March 2020]. JAMA Intern Med **2020**. doi:10.1001/jamainternmed.2020.0994.

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