**Title**: Corticosteroids in patients with COVID-19: what about the control group?

**Authors**: Tomasz Chroboczek[1], Marie Lacoste[1], Chloe Wackenheim[1], Thibaut Challan-Belval[1], Benjamin Amar[2], Thomas Boisson[2], Jason Hubac[2], Dominique Leduc[1], Colleen Masse[1], Victor Dechaene[1], Laetitia Touhiri-Maximin[1], Sandrine Megessier[1], Camille Lassale[3,4].

Affiliations:

[1] Service de maladies infectieuses et tropicales, Centre Hospitalier Alpes Léman, 558 route de Findrol, 74130 Contamine sur Arve, France

[2] Service de médecine Interne, Centre Hospitalier Alpes Léman, 558 route de Findrol, 74130 Contamines sur Arve, France

[3] Hospital del Mar Medical Research Institute (IMIM), Carrer Dr Aiguader, 88, 08003 Barcelona, Spain

[4] Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London WC1E 6BT, United Kingdom

Corresponding author: Tomasz Chroboczek

ORCID ID : https://orcid.org/0000-0001-8449-085X

Mail: tchroboczek@gmail.com

Tel: (0033) 0450823057 / Fax : (0033) 0450823029

Dear Editor.

Effect of corticosteroids in COVID-19 still needs to be examined [1-3]. In their article, Fadel et al. compared two groups of patients hospitalized with COVID-19, with over half of them receiving corticotherapy in both groups (68.2%, vs 56.8% p=0.094), but different median time between hospitalization and therapy initiation (2 days, IQR 1-3, vs 5 days , IQR 3-7). Negative evolution of the disease occurred less often in the early group (34.9 vs 54.3%, p=0.005). 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 more than 3L of oxygen, in adult patients hospitalized between 10 March and 9 April, 2020. The outcome of interest was oro-tracheal 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). In order 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, BMI>25 kg/m$^2$, hypertension, time from initiation of symptoms to hospitalization>7 days, CRP>150 mg/L, oxygen>3L, 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.

Out of 70 cases, 35 (50%) required mechanical ventilation, due to respiratory failure. Corticotherapy affected the risk of intubation with a risk difference (ATE) of -47.1% (95%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 that did not receive corticosteroids, 32, i.e. 65%, were intubated. Based on these results, systematic corticotherapy may have resulted in 65% - 47.1% =17.9%, i.e. 12 intubations overall. That would have lifted the pressure on the limited number of beds at the ICU 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's onset that presents a practical interest. This information is rarely found in other comparative studies [4, 6-9].

Further studies are urgently needed, in order 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.

**Contribution**: All authors have seen and approved the manuscript, and contributed significantly to the work.

**Acknowledgments**

Authors are grateful to Juliusz Chroboczek for his help with proof-reading. An early version of the text in pdf version has been sent on the preprint server MedRxiv.org.

**Conflict of interest and funding sources**

No financial support was received, and none of the authors has a conflict of interest concerning this report.

**References**


1. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet **2020**; 395(10223): 473-5.
2. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet **2020**; 395(10229): 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. Clin Infect Dis **2020**. https://doi.org/10.1093/cid/ciaa478
4. Fadel R, Morrison Austin R, Vahia A, et al. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19. Clinical Infectious Diseases **2020**. https://doi.org/10.1101/2020.05.04.20074609
5. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. Am J Epidemiol **2006**; 163(12): 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**. https://doi.org/10.5694/mja2.50577
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 **2020**: 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(1): 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. JAMA Intern Med **2020**. https://doi.org/10.1001/jamainternmed.2020.0994

**Table 1: Multivariable odds ratios of intubation associated with patients characteristics, n=70**

| | Odds Ratio (95% CI) | *p* |
|---|---|---|
| Age | 1.12 (0.98 to 1.29) | 0.105 |
| Sex | 0.18 (0.01 to 4.71) | 0.303 |
| Charlson index > 1 | 9.52 (0.55 to 164.42) | 0.121 |
| BMI[a] $\geq$ 25 kg/m$^{-2}$ | 1.34 (0.06 to 29.28) | 0.852 |
| High blood pressure | 4.18 (0.44 to 39.81) | 0.213 |
| Duration before hospitalization > 7d | 0.36 (0.032 to 4.17) | 0.416 |
| Oxygen dose at entrance > 3 l/mn | 54.69 (2 to 1497.49) | 0.018 |
| Highest CRP[b] > 150 mg/L | 73.47 (2.37 to 2277.84) | 0.014 |
| Azythromycine | 0.36 (0.02 to 5.19) | 0.451 |
| Hydroxychloroquine | 99.36 (1.67 to 5907.55) | 0.027 |
| Corticosteroids | < 0.001 (3.24e$^{-06}$ to 0.09) | 0.004 |

[a]BMI: Body Mass Index; CRP[b]: C-Reactive Protein