Corticosteroid-related in-hospital hyperglycemia: does it negate mortality benefits in COVID-19?

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Dear Editor,

We read with interest the randomised controlled trial evaluating the effectiveness of methylprednisolone in patients hospitalized with coronavirus disease 2019 (COVID-19) [1]. The findings from the trial revealed no mortality benefits with the use of methylprednisolone compared to a placebo in hospitalized COVID-19 patients. Importantly, there was also no mortality benefits observed in the subsets of patients who required invasive mechanical ventilation and non-invasive oxygen therapy. The findings were in stark contrast to RECOVERY trial [2] which reported that dexamethasone significantly reduced the mortality risk by 17% in hospitalized COVID-19 patients, by 18% in the subsets of patients who required non-invasive oxygen therapy, and by 36% in the subsets of patients who required invasive mechanical ventilation.

Further analysis of the trial observed a slightly higher median blood glucose level at baseline among patients randomized to methylprednisolone (200.3 mg/dL) compared to their counterparts randomized to placebo (195.2 mg/dL). Although such observation did not register a statistical difference between the two groups, we noticed that the interquartile range of blood glucose level was higher in the methylprednisolone group (88.6 mg/dL versus 86.9 mg/dL), which suggests the possibility that the patients in the methylprednisolone group may be at uncontrolled glycemic state. This was further substantiated by the observation that the proportion of patients in the methylprednisolone group who required insulin therapy was higher than that in the placebo group (59.5% versus 49.4%).

Hyperglycemia has been an independent predictor of mortality in hospitalized patients with COVID-19 [3]. Since hyperglycemia can be further worsened by the administration of systemic corticosteroids, the possibility for hyperglycemia to negate the mortality benefits from systemic corticosteroids cannot be ruled out [4]. In fact, the neutral findings on the risk of mortality with the use of methylprednisolone in this randomised controlled trial suggest such a possibility.

Within the limited literature focusing on the management of corticosteroid-related in-hospital hyperglycemia, there is one randomized, open-labeled, parallel-arm trial [5] which included 67 patients compared the efficacy of two protocols for the management of hyperglycemia related to systemic corticosteroids, namely the standard basal-bolus insulin protocol and correctional insulin protocol which aimed to match the glycemic profile of the particular systemic corticosteroids administered with or without basal-bolus insulin. Compared to patients who randomized to standard basal-bolus insulin protocol, those who randomized to correctional insulin protocol reported significantly lower mean blood glucose and glycemic variability.

Patients who received methylprednisolone are likely to develop hyperglycemic peak after 4-6 hours of administration of methylprednisolone [6]. The use of insulin neutral protamine Hagedorn as correctional insulin which has a peak effect coincides with the hyperglycemic peak of methylprednisolone is likely to dampen the hyperglycemia [7]. By similar analogy, the glycemic effect of dexamethasone which may last as long as 48 hours may require coverage with insulin glargine which has a glucose-lowering effect lasting more than 24 hours [8,9]. Therefore, clinicians who decide for systemic corticosteroid treatment in their patients with COVID-19 should anticipate the occurrence of hyperglycemia and manage upon pre-emptively, preferably based on the glycemic profile of the particular systemic corticosteroid.

Declarations of interest: None

References

1. Jeronimo CMP, Farias MEL, Val FFA, et al. Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (Metcovid): A Randomised, Double-Blind, Phase IIb, Placebo-Controlled Trial [published online ahead of print, 2020 Aug 12]. Clin Infect Dis. 2020;ciaa1177.
2. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report [published online ahead of print, 2020 Jul 17]. N Engl J Med. 2020;NEJMoa2021436.
3. Sardu C, D'Onofrio N, Balestrieri ML, et al. Outcomes in Patients With Hyperglycemia Affected by COVID-19: Can We Do More on Glycemic Control?. Diabetes Care. 2020;43(7):1408-1415.
4. Zayed Y, Barbarawi M, Ismail E, et al. Use of glucocorticoids in patients with acute respiratory distress syndrome: a meta-analysis and trial sequential analysis. J Intensive Care. 2020;8:43.
5. Lakhani OJ, Kumar S, Tripathi S, Desai M, Seth C. Comparison of Two Protocols in the Management of Glucocorticoid-induced Hyperglycemia among Hospitalized Patients. Indian J Endocrinol Metab. 2017;21(6):836-844.
6. Seggelke SA, Gibbs J, Draznin B. Pilot study of using neutral protamine Hagedorn insulin to counteract the effect of methylprednisolone in hospitalized patients with diabetes. J Hosp Med. 2011;6(3):175-176.
7. Donner T, Sarkar S. Insulin – Pharmacology, Therapeutic Regimens, and Principles of Intensive Insulin Therapy. [Updated 2019 Feb 23]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. Available from: https://www.ncbi.nlm.nih.gov/books/NBK278938/
8. Low Wang CC, Draznin B. Practical approach to management of inpatient hyperglycemia in select patient populations. Hosp Pract (1995). 2013;41(2):45-53.
9. Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. Diabetes Care. 2000;23(5):644-649.