Comment on the "Use of intravenous immunoglobulin for the treatment of severe COVID-19"

Dear Editor

The publication titled "Use of intravenous immunoglobulin for the treatment of severe COVID-19 in the Chris Hani Baragwanath Academic Hospital intensive care unit, Johannesburg, South Africa [1]" provides valuable information on the use of high-dose intravenous immunoglobulin (IVIg) in severe COVID-19 pneumonia, as well as a detailed comparison between patients receiving IVIg and those receiving standard therapy. However, despite presenting useful data, there remain areas for constructive critique and further investigation.

A key limitation is the absence of a randomised controlled trial (RCT) design. While the study offers helpful observations, its retrospective nature limits the ability to control for confounding variables and potential biases that may have influenced outcomes. A well-conducted RCT would mitigate random variation and treatment allocation bias, thereby providing more definitive evidence regarding the efficacy of IVIg in this setting.

One notable finding was the lack of significant differences between the IVIg and standard-of-care groups across various clinical measures, including inflammatory markers (C-reactive protein), organ dysfunction (SOFA score), and oxygenation (P/F ratio). These results suggest that while IVIg shows potential, it did not significantly change the clinical trajectory of the disease compared with standard treatment. Additionally, as there were no significant differences in outcomes such as duration of ventilatory support, complication rates, or mortality, it may be necessary to investigate other factors influencing therapeutic response. For example, the study only briefly addressed risks such as hospital-acquired infections and thrombosis. The potential role of IVIg in preventing these common secondary complications in severe COVID-19 warrants further exploration.

Furthermore, the study did not provide detailed insight into the duration of IVIg therapy, which may meaningfully influence treatment efficacy. To strengthen future research, investigations could assess the mechanisms by which IVIg modulates inflammation and immune responses, particularly in the context of the cytokine storm characteristic of severe COVID-19. Understanding how IVIg interacts with immune pathways to alter cytokine activity or enhance immunological tolerance may lead to improved therapeutic strategies. Additionally, exploring the role of IVIg in preventing or reducing long-term post-acute sequelae of SARS-CoV-2 infection (PASC) is a promising avenue. Determining whether IVIg reduces the incidence or severity of PASC-related complications may yield further clinical opportunities.

Looking ahead, larger and more diverse prospective studies - ideally multicentre RCTs -should examine the potential benefits of using IVIg in combination with emerging therapies such as antivirals and immunomodulatory agents. The incorporation of biomarkers of immune activation and tissue injury may help more accurately identify patient subgroups most likely to benefit from IVIg therapy. Moreover, considerations of cost-effectiveness and long-term outcomes will be essential in determining the appropriateness of IVIg implementation in clinical practice. Given the continual evolution of the pandemic and the emergence of new viral variants, further research into adjuvant therapies such as IVIg remains critical for improving outcomes in future COVID-19 surges and other severe viral respiratory illnesses.

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1. Mensky G, van Blydenstein A, Damelin J, Omar S. Use of intravenous immunoglobulin for the treatment of severe COVID-19 in the Chris Hani Baragwanath Academic Hospital intensive care unit, Johannesburg, South Africa. *South Afr J Crit Care* 2024;40(3):e1897. https://doi.org/10.7196/SAJCC.2024.v40i3.1897