

Dose-response Association Between Magnesium Sulfate Administration and 28-Day Mortality in ICU Patients With Delirium: A Target-trial Emulation

Wen-qing Nie, Ze-lin Liu, Rui-chen Wang*

School of Sports Science, Qufu Normal University, Jining, China

Email address:

2297710183@qq.com (Wen-qing Nie), 3492591086@qq.com (Ze-lin Liu), W_Ruichen@163.com (Rui-chen Wang)

*Corresponding author

Abstract

Background: Delirium is a frequent and clinically consequential manifestation of acute brain dysfunction in critically ill patients, yet no pharmacological strategy has consistently improved survival. Magnesium sulfate is biologically plausible as a neuroprotective adjunct through N-methyl-D-aspartate receptor modulation, calcium influx inhibition, and anti-inflammatory effects, but its clinical relevance in ICU delirium remains uncertain. **Objective:** To evaluate the association between intravenous magnesium sulfate administration and 28-day mortality among ICU patients with delirium, and to explore dose-response patterns, baseline magnesium status, and hemodynamic safety. **Methods:** We performed a target-trial emulation using the Medical Information Mart for Intensive Care IV database. Adult patients with ICU delirium were classified according to magnesium sulfate exposure during the index ICU stay. Propensity scores were estimated using generalized boosted models, followed by 1:1 matching to construct a balanced cohort. Doubly robust estimation was used for the primary analysis. Restricted cubic splines assessed the association between cumulative magnesium sulfate dose and 28-day mortality, truncated at the 99th percentile to reduce the influence of sparse extreme values. Prespecified subgroup and safety analyses examined baseline magnesium status and new-onset hypotension requiring vasoactive therapy. **Results:** Among 40,287 eligible patients, 20,256 were included after matching, with 10,128 patients in each group. Magnesium sulfate administration was associated with lower 28-day mortality in the doubly robust model (adjusted odds ratio, 0.72; 95% confidence interval, 0.65–0.79; $p < 0.001$). Dose-response analysis suggested an approximately linear inverse association across the cumulative dose range of 0–30 g, without significant evidence of non-linearity. The association persisted among patients with baseline normomagnesemia, suggesting that the observed signal may not be explained solely by correction of hypomagnesemia. Magnesium sulfate was not significantly associated with new-onset hypotension requiring vasoactive therapy. **Conclusion:** In this large real-world ICU delirium cohort, magnesium sulfate administration was associated with lower 28-day mortality, with supportive dose-response and safety signals. These findings identify magnesium sulfate as a promising, low-cost candidate intervention for prospective trials in ICU delirium.

Keywords

Delirium, Magnesium Sulfate, Intensive Care Unit, Mortality, Target-trial Emulation, Dose-response Association