INPLASY

The Effects of Intravenous Glutamine Supplementation in Critically Ill Patients: A Systematic Review and Meta-Analysis

INPLASY202540046

doi: 10.37766/inplasy2025.4.0046

Received: 15 April 2025

Published: 15 April 2025

Kwon, IG; Baik, SM, Lee, JG.

Corresponding author:
Jae Gil Lee

jakii71@gmail.com

Author Affiliation:
Ewha Womans University Mokdong Hospital.

ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202540046

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 April 2025 and was last updated on 15 April 2025.

INTRODUCTION

Review question / Objective To evaluate the effects of IV glutamine supplementation on clinical outcomes in critically ill adult patients.

Rationale Glutamine is a conditionally essential amino acid that plays a pivotal role in cellular metabolism, nitrogen balance, and immune function, particularly in critically ill patients. During critical illness, endogenous glutamine production is often insufficient to meet increased metabolic demands, leading to plasma glutamine depletion. This deficiency has been associated with impaired immune responses, increased susceptibility to infections, and adverse clinical outcomes in ICU patients.

Intravenous (IV) glutamine supplementation has been proposed to restore glutamine levels and potentially improve clinical outcomes in this population. However, the efficacy and safety of IV glutamine supplementation remain subjects of ongoing debate. While some randomized controlled trials (RCTs) have reported benefits such as reduced infection rates, decreased pneumonia incidence, or shortened duration of mechanical ventilation, others have found no significant impact on mortality or have even suggested potential harm, particularly in patients with multiple organ failure.

Clinical practice guidelines have evolved in response to this conflicting evidence. The European Society for Clinical Nutrition and Metabolism (ESPEN) and the American Society for Parenteral and Enteral Nutrition (ASPEN) now recommend against the routine use of glutamine supplementation in critically ill patients, except in specific cases such as burns or trauma. These changes highlight the need for updated, high-quality evidence to inform clinical decision-making.

Previous meta-analyses have often combined data from both enteral and parenteral glutamine administration, making it difficult to isolate the effects of IV supplementation. In addition, variation

in study design, patient populations, and supplementation protocols further complicate interpretation. Therefore, a systematic review and meta-analysis that focuses exclusively on IV glutamine supplementation in critically ill adult patients is essential to clarify its clinical effects.

Condition being studied Critically ill adult patients in the intensive care unit (ICU).

METHODS

Search strategy A comprehensive literature search was conducted in the following databases: Ovid MEDLINE, Embase, Cochrane Library, and KoreaMed. The search was performed up to August 2023, using both MeSH terms and free-text keywords related to:

"glutamine"

"intravenous"

"critically ill"

"intensive care"

"randomized controlled trial"

Filters were applied to limit results to RCTs in human adults.

Participant or population Critically ill adult patients (≥18 years old) admitted to the intensive care unit (ICU), including those with conditions such as sepsis, trauma, or postoperative complications, receiving or eligible for intravenous nutrition support.

Intervention Intravenous (IV) glutamine supplementation administered as part of parenteral nutrition or as an adjunct therapy in critically ill adult patients.

Comparator Standard care or placebo without intravenous glutamine supplementation.

Study designs to be included Randomized controlled trials (RCTs) only.

Eligibility criteria
Inclusion criteria:
- Randomized controlled trials (RCTs)
- Adult patients (≥18 years) admitted to the ICU
- Studies evaluating intravenous (IV) glutamine supplementation
- Reporting at least one clinical outcome (e.g., mortality, infection, ICU or hospital length of stay, mechanical ventilation duration)

Exclusion criteria:
- Studies focusing exclusively on enteral glutamine supplementation
- Studies with combined enteral and IV glutamine without separate IV data
- Non-randomized studies, observational studies, reviews, abstracts, or case reports
- Studies involving non-critically ill populations or lacking relevant clinical outcomes.

Information sources The following electronic databases were searched: Ovid MEDLINE, Embase, Cochrane Library, and KoreaMed.
The search included studies published from inception to August 2023.
Reference lists of included articles were also manually reviewed to identify additional eligible studies.

Main outcome(s) Overall mortality in critically ill adult patients receiving intravenous glutamine supplementation.

Additional outcome(s)
In-hospital mortality
Nosocomial infections (e.g., pneumonia, bloodstream infections, urinary tract infections, wound infections)
ICU length of stay (ICU-LOS)
Hospital length of stay (H-LOS)
Duration of mechanical ventilation (MV).

Data management Data were extracted independently by two reviewers using a standardized data extraction form. Extracted data included study characteristics, participant details, intervention and comparator information, and clinical outcomes. Discrepancies were resolved through discussion or consultation with a third reviewer. Data were managed using Microsoft Excel and analyzed with Review Manager (RevMan) software.

Quality assessment / Risk of bias analysis The quality of included studies was assessed using the Cochrane Risk of Bias (ROB) 2.0 tool. Two reviewers independently evaluated each study across key domains: random sequence generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, and selective reporting. Disagreements were resolved by consensus or through a third reviewer. The overall risk of bias was categorized as low, some concerns, or high.

Strategy of data synthesis Data were synthesized using meta-analysis with a random-effects model (DerSimonian and Laird method) to account for between-study variability. Odds ratios (ORs) were calculated for dichotomous outcomes, and mean differences (MDs) for continuous outcomes, both with 95% confidence intervals (CIs). Statistical heterogeneity was assessed using the I^2 statistic, with values above 50% considered substantial. Sensitivity analyses were performed by excluding studies with a high risk of bias. Data synthesis was conducted using Review Manager (RevMan) version 5.4.

Subgroup analysis Subgroup analysis was initially planned based on patient characteristics (e.g., trauma vs. sepsis), glutamine dose, and duration of supplementation. However, due to substantial variability in study protocols and limited subgroup-specific data, formal subgroup analyses could not be performed.

Sensitivity analysis Sensitivity analyses were conducted by excluding studies with a high risk of bias to assess the robustness of the main findings. The results remained consistent, indicating that the overall conclusions were not significantly influenced by these studies.

Language restriction Only studies published in English were included.

Country(ies) involved Republic of Korea (South Korea).

Other relevant information This review was conducted in accordance with PRISMA guidelines. Although the protocol was not registered prior to conducting the review, all methods—including literature search, data extraction, risk of bias assessment, and statistical analysis—were predefined and transparently reported in the manuscript.

Keywords Critical Illness; Glutamine; Parenteral nutrition; Meta-Analysis; Intensive Care Unit.

Dissemination plans The findings of this systematic review and meta-analysis will be disseminated through publication in a peer-reviewed journal and presentation at relevant academic conferences in the fields of critical care and clinical nutrition.

Contributions of each author

Author 1 - In Gyu Kwon - In Gyu Kwon contributed to the study concept and design, data acquisition, statistical analysis, interpretation of data, and drafting of the manuscript. He also participated in study supervision and took responsibility for ensuring the accuracy and integrity of the work.
Email: surgeon@yuhs.ac
Author 2 - Seung Min Baik - Seung Min Baik contributed to drafting the manuscript, revising it critically for important intellectual content, and finalizing the manuscript for submission.
Email: baiksm@ewha.ac.kr
Author 3 - Jae Gil Lee - Jae Gil Lee contributed to the study concept and design, data acquisition, statistical analysis, interpretation of data, and drafting of the manuscript. He also provided study supervision, participated in critical revision of the manuscript, and ensured the accuracy and integrity of the entire work.
Email: jakii71@gmail.com