INPLASY PROTOCOL

To cite: Qu et al. The effect of balanced crystalloids versus normal saline in critically ill patients: a systematic review and meta-analysis. Inplasy protocol 2022110154. doi: 10.37766/inplasy2022.11.0154

Received: 30 November 2022

Published: 30 November 2022

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Support: **Not applicable.**

Review Stage at time of this submission: **Piloting of the study selection process.**

Conflicts of interest:
None declared.

The effect of balanced crystalloids versus normal saline in critically ill patients: a systematic review and meta-analysis

Qu, J[1]; Xu, XY[2]; Zhang, K[3]; Hu, LH[4].

Review question / Objective: **The optimal resuscitative fluid for critically ill patients remains controversial. In this meta-analysis, we aimed to compare the effect of balanced crystalloids versus normal saline on clinical outcomes for critically ill adult patients.**
Eligibility criteria: **The inclusion criteria were as follows: 1. Population: critically ill adult patients; 2. Intervention: the use of balanced crystalloids with a near-physiological chloride concentration (e.g., Lactated Ringer's, Plasma-Lyte 148); 3. Comparison: the use of normal saline, defined as 0.9% saline with a chloride content of 154 mmol/L; 4. Outcomes: primary outcome was overall mortality, including ICU mortality, in-hospital mortality, and 28/30-day mortality. Secondary outcomes were incidence of AKI (defined as KDIGO stage II or higher[17]), and need for new RRT; 5. Design: randomized trials.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 November 2022 and was last updated on 30 November 2022 (registration number INPLASY2022110154).

INTRODUCTION

Review question / Objective: **The optimal resuscitative fluid for critically ill patients remains controversial. In this meta-analysis, we aimed to compare the effect of balanced crystalloids versus normal saline on clinical outcomes for critically ill adult patients.**

Condition being studied: **Intravenous fluid therapy is one of the most commonly used intervention in intensive care unit (ICU), especially for critically hypotensive patients[1]. The crystalloid fluids are**

recommended as the preferred fluid for initial resuscitation, especially for patients with sepsis and septic shock[2, 3]. On the other hand, rapid infusion of a large volume of crystalloid solutions with non-physiological content may result in electrolyte disorder, hyperchloremia, and metabolic acidosis, which can further cause clinical complications such as severe renal, cardiac or hepatic injury[4, 5].

For decades, the normal saline (0.9% sodium chloride solution) has been the most commonly administered crystalloid solution in critically ill patients worldwide[6, 7]. More recently, emerging evidence raises concerns that the use of normal saline may lead to increased acidemia, reduced renal blood flow and urine output[4], which may eventually result in acute kidney injury (AKI) [8-10] and death[11, 12]. Since the high chloride content of normal saline may lead to possible adverse effects, balanced crystalloids, in which chloride anions are replaced by lactate or acetate, are increasingly used alternatives[13]. Compared to normal saline, the chemical composition of balanced crystalloids are more similar to that of human plasma, which involve less chloride and have a higher in vivo strong ion difference[1].

However, two recently completed large randomized controlled trials (RCTs): PLUS (Plasma-Lyte 148 versus Saline) trial[14] and BaSICS (Balanced Solutions in Intensive Care Study) trial[15] have compared the balanced crystalloids to normal saline among more than 15,000 critically ill patients. The results no significant difference on concerned clinical outcomes including the overall mortality, incidence of AKI, and need for new RRT between the two crystalloid solutions. At present, the preferred choice between normal saline and balanced crystalloids in critically ill patients remains a subject of debate. In view of the widespread use of intravenous fluids therapy worldwide, even small differences between the choice of fluids and their relevance to clinical outcomes will have a significant clinical impact. Therefore, the purpose of this updated meta-analysis was to assess the effects of balanced solution versus 0.9% saline solution on clinical outcomes in critically ill patients.

METHODS

Search strategy: #1 Intensive Care Units [MeSH Terms] OR Critical Care [MeSH Terms] OR Critical Illness [MeSH Terms] OR icu [Title/Abstract] OR Critical Care [Title/Abstract] OR critically ill [Title/Abstract] OR Intensive Care [Title/Abstract]
#2 buffered [Title/Abstract] OR balanced [Title/Abstract] OR Plasmalyte [Title/Abstract] OR Ringer's Lactate [Title/Abstract] OR lactated Ringer's [Title/Abstract] OR Ringer's Lactate [MeSH Terms]
#3 Saline Solution [MeSH Terms] OR Sodium Chloride [MeSH Terms] OR Saline Solution [Title/Abstract] OR Sodium Chloride [Title/Abstract] OR Saline [Title/Abstract] OR 0.9% NaCl [Title/Abstract]
#4 randomized controlled trial [MeSH Terms] OR random* [Title/Abstract]
#1 AND #2 AND #3 AND #4.

Participant or population: Critically ill adult patients.

Intervention: The use of balanced crystalloids with a near-physiological chloride concentration (e.g., Lactated Ringer's, Plasma-Lyte 148).

Comparator: The use of normal saline, defined as 0.9% saline with a chloride content of 154 mmol/L.

Study designs to be included: Randomized controlled trials.

Eligibility criteria: The inclusion criteria were as follows: 1. Population: critically ill adult patients; 2. Intervention: the use of balanced crystalloids with a near-physiological chloride concentration (e.g., Lactated Ringer's, Plasma-Lyte 148); 3. Comparison: the use of normal saline, defined as 0.9% saline with a chloride content of 154 mmol/L; 4. Outcomes: primary outcome was overall mortality, including ICU mortality, in-hospital mortality, and 28/30-day mortality. Secondary outcomes were incidence of

AKI (defined as KDIGO stage II or higher[17]), and need for new RRT; 5. Design: randomized trials.

Information sources: We performed a literature search for eligible RCTs in English in four electronic databases (PubMed, Embase, Scopus, and Cochrane Library) from inception through November 20th, 2022.

Main outcome(s): Primary outcome was overall mortality, including ICU mortality, in-hospital mortality, and 28/30-day mortality.

Additional outcome(s): Secondary outcomes were incidence of AKI (defined as KDIGO stage II or higher[17]), and need for new RRT.

Quality assessment / Risk of bias analysis: The Cochrane risk of bias tool[18] was utilized for assessing the methodological quality of including studies by two authors (), any differences in opinion were resolved by a third adjudicator.

Strategy of data synthesis: We computed the pooled odds ratio (OR) with 95% confidence interval (CI) for outcomes. The heterogeneity between studies was assessed by the Higgins inconsistency (I2) statistics[19], substantial heterogeneity was identified when I2 value>30%. In consideration of the significant difference in sample size between included studies, the random effect model was employed to perform the analysis. In addition, publication bias was assessed by using the funnel plot and Egger's regression test[20].

Subgroup analysis: Predefined subgroup analyses stratified by population (sepsis or traumatic brain injury), types of balanced crystalloids (Lactated Ringer's solution, Plasma-Lyte, or others) were performed to investigate the potential source of heterogeneity.

Sensitivity analysis: A sensitivity analysis was conducted to explore the effect of individual study by consecutive exclusion of each study.Predefined subgroup analyses stratified by population (sepsis or traumatic brain injury), types of balanced crystalloids (Lactated Ringer's solution, Plasma-Lyte, or others) were performed to investigate the potential source of heterogeneity.

Language restriction: English.

Country(ies) involved: China.

Keywords: balanced crystalloids; normal saline; critically ill; meta-analysis.

Contributions of each author:

Author 1 - jing qu - Author 1 conceived the idea, performed the analysis, and drafted the initial writing of this manuscript.
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