Balanced Crystalloids versus Normal Saline as Intravenous Fluid Therapy among Critically Ill patients: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Introduction: Recent studies on critically ill adults has shown that use of normal saline with its supraphysiologic chloride content has been associated with an increased incidence of hyperchloremic metabolic acidosis, acute kidney injury (AKI), renal replacement therapy (RRT), hypotension and death. The objective of this meta-analysis was to assess the clinical outcomes associated with the use of balanced crystalloids versus normal saline solution.

Methods: We searched PubMed/MEDLINE, Embase and Cochrane Library (CENTRAL) databases in accordance with PRISMA guidelines. Our inclusion criteria were the following: randomized controlled trials, adult critically ill patients, comparisons between patients receiving either balanced crystalloids (lactated ringer's solution, plasma-lyte) or normal saline, and at least one endpoint that measure intensive care unit mortality, risk of AKI (defined as stage 2 or greater in the RIFLE criteria) and risk of RRT. Risk ratios (RRs) and confidence intervals (C.I) were calculated via Review Manager Version 5.3 using the fixed-effect modelling.

Results: A total of four randomized controlled trials, which were all assessed to be good quality and low risk of bias, with 19,105 patients were included. Use of balanced crystalloids showed a trend towards lower incidence of AKI (RR 0.94, 95% C.I (0.87-1.02), *P*=0.69), RRT use (RR 0.91, 95% C.I. (0.77-1.07), *P*=0.29) and ICU mortality (RR 0.91, 95% C.I. (0.82-1.01), *P*=0.95). There is no significant heterogeneity identified.

Conclusion: Use of balanced crystalloids as intravenous fluid therapy among critically ill patients demonstrated a trend toward lower incidence of AKI, RRT and ICU mortality, compared to normal saline solution.

Keywords: intravenous fluids, acute kidney injury, critical illness

Introduction

Intravenous fluid therapy with crystalloids is among the most common medical interventions in the intensive care unit; with normal saline solution as the most commonly used crystalloid for fluid resuscitation worldwide.[1-4] The composition of normal saline is, however, far from being physiologic as its higher chloride content (approximately 1.5 times that of plasma)[2] may be a risk for the development of acute kidney injury (AKI) through various mechanisms including primarily hyperchloremic metabolic acidosis, decreased renal cortical perfusion, decreased renal blood flow, and immune dysfunction and gastrointestinal dysfunction, among others.[5] Alternatives to normal saline solution include balanced crystalloids such as ringer's lactate (hartmann's solution) and plasmalyte 148, as both of these fluids have compositions with closer resemblance in composition to that of normal plasma.[1]

Many observational studies have shown that balanced crystalloids may be associated with a decreased risk for AKI, requirement for renal replacement therapy (RRT) and mortality compared to normal saline.[6-9] Furthermore, a retrospective study showed that peri-operative fluid resuscitation using plasma-lyte had decreased incidence of sepsis, need for blood transfusions, AKI, RRT requirements.[10] Despite these benefits, however, evaluation of the full extent of effects of administering balanced crystalloids in the critical care setting remains limited to a few randomized trials; as these trials have showed conflicting results, with a majority of the trials showing no difference in clinical outcomes: mortality, AKI, and RR;T[1-3] while the largest and most recent among the trials showed benefit on giving balanced crystalloids instead of normal saline.[4]

We performed a meta-analysis of all randomized trials comparing the effects of balanced crystalloids versus normal

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saline in fluid resuscitation of critically ill adults admitted to the intensive care unit. Our study aims to determine whether the use of balanced crystalloids versus normal saline has an effect on clinical outcomes: mortality, risk of developing AKI and requirement for RRT.

Methods

Search Methods for Identification of Studies

Electronic searches

A highly sensitive search strategy (Appendix A) was used for identifying randomized controlled trials. Both electronic and manual means of retrieving relevant studies were performed. Electronic searches (search strategy not limited by language and publication status) were completed of PUBMED, MEDLINE (January 2014 to June 2018; National Library of Medicine, Bethesda, USA), EMBASE (1974 to June 2018; Elsevier Science, New York, USA), Cochrane Central Register of Controlled Trials, Cochrane Kidney and Transplant register of Studies, Google Scholar, and Research Gate. The reference lists of all identified papers were searched for further information.

Other resources

Manual searches were also conducted in Google Scholar and http://www.researchgate.net. In addition, for articles that were either unpublished or full-text not available in the internet, the authors were contacted via their respective emails.

Selection Criteria

The researchers included randomized controlled trials, and comparisons between patients receiving either balanced crystalloids or normal saline, and at least one endpoint that measure mortality, risk of AKI and risk of RRT.

Data extraction

The two independent reviewers (JRC and HHC) assessed the quality of the studies based on the criteria provided in the Cochrane Handbook for Systematic Reviews of Interventions; the results of these individual assessments were then compared by a third and independent reviewer (JPB). In cases in which the assessments varied, these differences were resolved by the third and independent reviewer. Studies were assessed as high-quality or low risk of bias if they fulfilled the following criteria: (1) treatment allocation was randomized with adequate concealment; (2) the treatment and control groups were balanced in terms of known determinants of outcome; (3) outcome assessment was done in a double-blind manner; (4) outcome detection methods used were similar for both groups; (5) treatment and control groups were treated equally in terms of other therapeutic and co-interventions received, frequency of follow-up and general quality of care; (6) an intention-to-treat analysis was conducted; and (7) drop-out rates between groups were comparable. On the other hand, studies were considered fair-quality or moderate risk of bias if any subtle biases were present, such as: (1) unclear allocation concealment; (2) absence of blinding; and (3) no intent-to-treat analysis. And lastly, studies were considered low-quality or high risk of bias if any of the frank biases was seen: (1) significant differences between the treatment and control group in terms of known predictors of outcome; (2) obvious differences in the general quality of care received by subjects in both groups; (3) marked difference in drop-out rates; and (4) outcome detection methods were different for both groups. Clinical outcomes examined were intensive care unit mortality, incidence of AKI (defined as stage 2 or greater in the RIFLE criteria), and incidence of RRT. Risk ratios (RRs) and confidence intervals were calculated via Review Manager Version 5.3 using the fixed-effect modelling.

Data analysis

All outcome measures were combined and analyzed using a fixed-effect model in Review Manager (Rev Man) Version 5.3. A 95% confidence interval was used. Outcomes were classified as dichotomous if the outcome is one of only two possible categorical responses. For dichotomous data, the risk ratio or the probability that an event will occur were determined for each comparison. A forest plot was constructed to show the overall effect of intervention against control in all the studies grouped together. Other outcomes such as adverse effects were presented as narratives.

Test for Heterogeneity

Heterogeneity can be interpreted as a percentage of total variation between studies that is attributable to heterogeneity rather than to chance. Heterogeneity was quantified using both the chi square test for heterogeneity with $p<0.10$ as the cut-off for significant heterogeneity as well as the I^2 test, i.e. $I^2 > 50\%$ suggests significant degree of heterogeneity or a value of 0% indicates no observed heterogeneity.

Results

Trial Inclusion

Twenty-nine potential studies were screened for possible inclusion into the analysis. However, twenty-five studies were excluded because they were either not-randomized, non-ICU setting or research study protocol only. A total of four studies with total population of 19,105 patients (n=9,647 in balanced crystalloids group and n=9,458 in Saline group) were included in the final analysis (Figure 1).

Characteristics of included studies

The four included studies were all multicenter randomized controlled trials. Two studies[2,3] served as pilot studies to bigger trial.[4] Balanced crystalloids used was either Lactated Ringers[3,4] or Plasmalyte-148. See Table I Characteristics of included studies. All studies were of good quality (Figure 2); two studies[3,4] were unblinded, simulating a pragmatic approach.

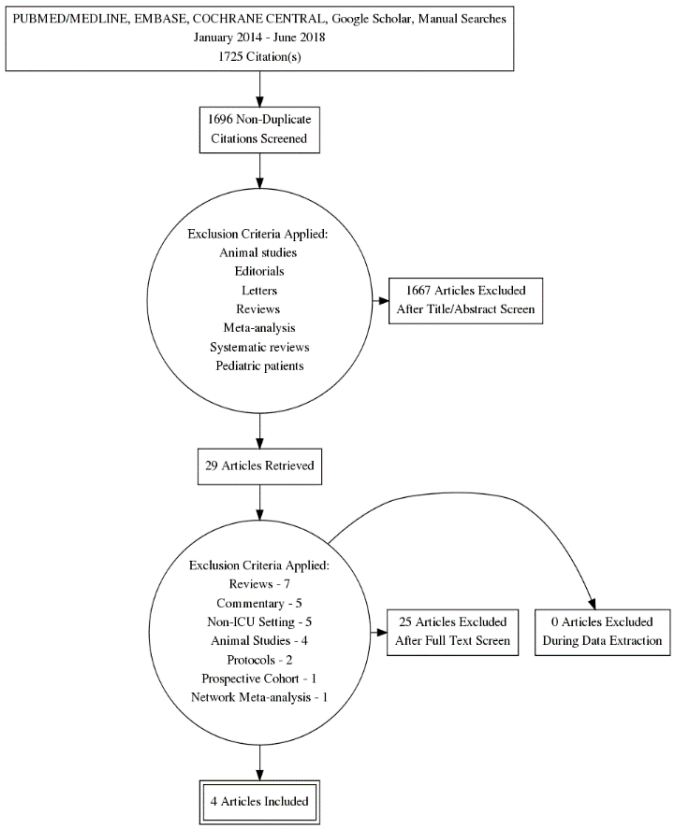

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) flow diagram of our literature search and study selection

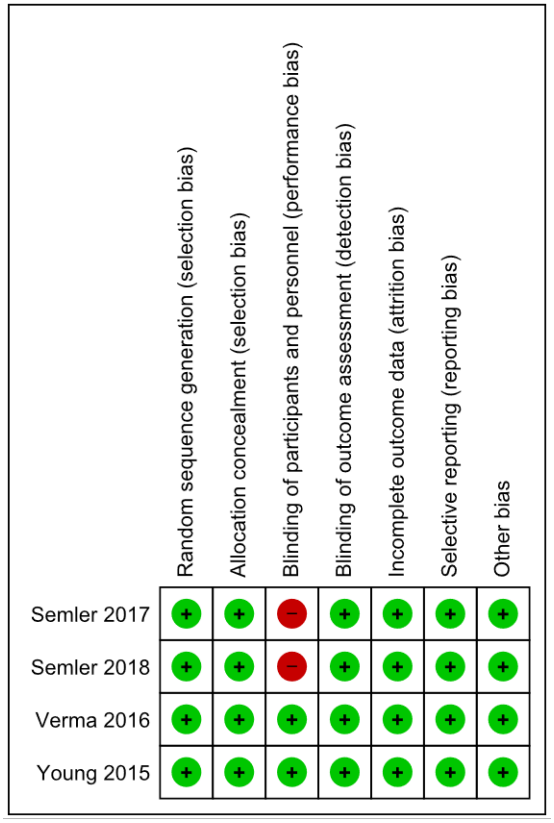

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Table I. Characteristics of included studies

Author/Year	Young (2015)	Verma (2016)	Semler (2016)	Semler (2018)
Title	Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury among Patients in the Intensive Care Unit The SPLIT Randomized Clinical Trial	A multicentre randomised controlled pilot study of fluid resuscitation with saline or Plasma-Lyte 148 in critically ill patients	Balanced Crystalloids versus Saline in the Intensive Care Unit: The SALT Randomized Trial	Balanced Crystalloids versus Saline in Critically Ill Adults
Design	Double-blind, cluster randomized, double-crossover trial	Multicenter, double-blind, randomized controlled trial	Cluster-randomized, multiple-crossover trial	Pragmatic, cluster-randomized, multiple-crossover trial
Randomization	Computer generated (clusters)	Computer generated (permuted blocks)	Computer generated (simple randomization)	Computer generated (clusters)
Allocation Concealment	Alternating blocks between crystalloid fluids	Sealed envelopes	Alternating blocks between crystalloid fluids	Alternating months: even-numbered months: saline, odd-numbered months: balanced crystalloids
Blinding	Patients, clinicians and investigators blinded Identical appearance of interventions	Patients, nurses and clinicians blinded Identical appearance of interventions	Patients and clinicians not blinded	Patients and clinicians not blinded
Outcomes	Incidence of AKI, RRT use; in-hospital mortality.	Daily base excess (BE), incidence of acute kidney injury (AKI), change in serum creatinine and serum chloride levels, and mortality.	Difference between study groups in the proportion of isotonic crystalloid administered that was saline, Major Adverse Kidney Events within 30 days (MAKE30) composite of death, dialysis, or persistent renal dysfunction.	Major adverse kidney event within 30 days, new renal-replacement therapy, or persistent renal dysfunction at hospital discharge or 30 days
Comparison	PL-148 (n = 1152) vs. Saline (n = 1110)	Saline (n = 34) vs. PL-148 (n = 33)	Saline (n=454) Vs. Lactated Ringer's solution or Plasma-Lyte A®) (n=520)	Lactated Ringer's solution or Plasma-Lyte A®) (N = 7942) Vs. Saline (N = 7860)
Follow-up	Intention-to-treat analysis Sensitivity analysis	Intention-to-treat analysis Sensitivity analysis	Intention-to-treat analysis Sensitivity analysis	Intention-to-treat analysis Sensitivity analysis
Trial Period	April – October 2014 Completed	July 16 – October 22, 2015 Completed	February 3 – May 31, 2015 Completed	June 1, 2015 – April 30, 2017 Completed
Trial Registry Number	www.clinicaltrials.gov (ACTRN12613001370796)	Australian New Zealand Clinical Trials Registry (ANZCTRN 12615000158561)	www.clinicaltrials.gov (NCT 02345486)	www.clinicaltrials.gov (NCT02444988 and NCT02547779)
Protocol Access	DOI:10.1001/jama.2015.12334	PMID:27604335	DOI:10.1164/rccm.201607-1345OC	DOI:10.1056/NEJMoa1711584

Study Outcomes

Incidence of AKI (stage II or greater)

Pooled analysis of the primary outcome comparing Balanced Crystalloids versus Saline showed a 6% reduction in the incidence of AKI (stage II or greater) (RR 0.94 95% C.I 0.87-1.02), (Figure 3) however the result is not statistically significant. There was no significant heterogeneity detected.

Use of RRT

Use of balanced crystalloids resulted into 9% reduction (RR 0.91 95% C.I. 0.77-1.07) in the incidence of RRT versus normal saline (Figure 4). No significant heterogeneity was detected

ICU mortality

Use of balanced crystalloids showed 9% reduction in ICU mortality versus normal saline (Figure 5), however this results were not statistically significant (RR 0.91 95% C.I 0.82 – 1.01).

Discussion

Intravenous fluids (IV) are commonly administered for hospitalized patients for treatment of shock and maintain general body hydration. The choice of type IV fluid to address losses from intravascular compartment, as well as external, or correct existing water/electrolyte deficits is inherently difficult. Normal saline solution is a crystalloid containing 0.9% sodium chloride (est. 150 meqs of sodium and chloride), which effectively increases circulatory volume during hypovolemia or stress, albeit can deliver excess sodium and chloride if used as maintenance fluid. It is theorized that excess chloride delivery to the macula densa may activate the tubuloglomerular feedback, which may trigger afferent arteriolar vasoconstriction, mesangial contraction, hence associated with reductions in glomerular filtration. This is supported by a recent RCT[5] which showed chloride-restrictive intravenous strategy is associated with a decrease in the incidence of the more severe stages of AKI and the use of RRT. However, the results of our meta-analysis seem to be in contrast with a recent meta-analysis in 2017 by Neto et al.[11] where the incidence of in-hospital mortality, AKI and need for RRT was not different between balanced solution and isotonic saline among postoperative patients. The differences in included population (postoperative renal transplant) might be confounding factor for the contrasting results.

This meta-analysis has several limitations; 1) the results were heavily influenced by two large trials, and 2) use of balanced crystalloids limited to lactated ringers solution

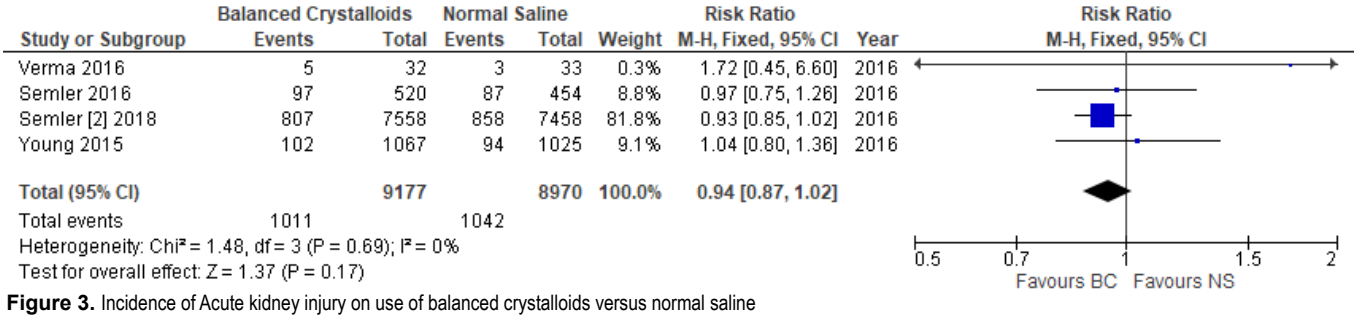

Figure 3. Incidence of Acute kidney injury on use of balanced crystalloids versus normal saline

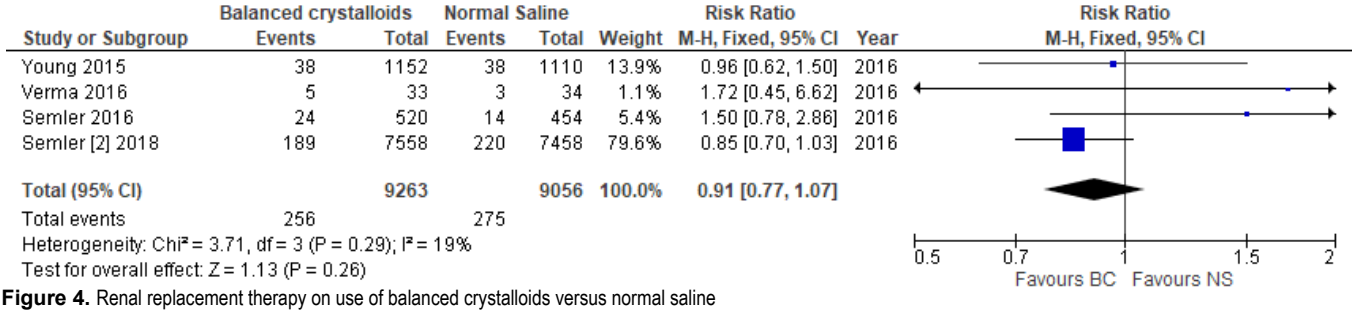

Figure 4. Renal replacement therapy on use of balanced crystalloids versus normal saline

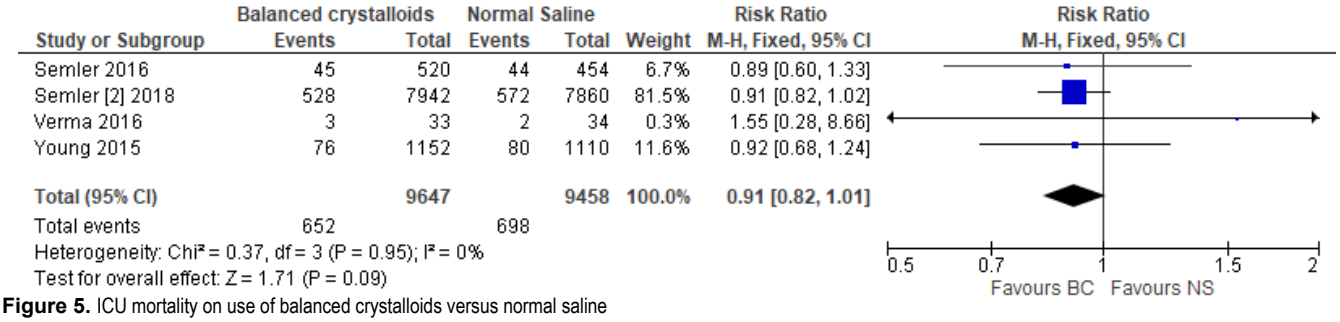

Figure 5. ICU mortality on use of balanced crystalloids versus normal saline

and plasmalyte. Whether the clinical effect is attributed to the low chloride content or the use of solution containing lactate or its buffer component, is still unknown. The results of this meta-analysis also seem to be in agreement with those of non-critically ill patients.[12]

Overall, the difference in the clinical outcomes of use of two types of intravenous fluid therapy might be small and statistically insignificant, however given that intravenous fluid therapy is one of the most common interventions, given to millions of patients each year, the overall clinical effect and renal outcomes of use of balanced crystalloids as intravenous fluid therapy among critically ill patients might still be clinically significant.

Conclusion

Among critically ill patients, the use of balanced crystalloids as intravenous fluid therapy demonstrated a trend toward lower incidence of AKI, RRT and ICU mortality, compared to normal saline solution. Further trials are needed with better blinding design of allocated intervention.

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Appendix A

Search Strategy

The search strategy combined the search terms "balanced crystalloids versus normal saline", "Plasma-Lyte 148 versus normal saline", "critically ill adults", "intensive care unit", "acute kidney injury", and "renal replacement therapy". The following search terms were used in the PUBMED search strategy: balanced(All Fields) AND crystalloids(All Fields) AND versus(All Fields) AND ("sodium chloride"(MeSH Terms) OR ("sodium"(All Fields) AND "chloride"(All Fields)) OR "sodium chloride"(All Fields) OR "saline"(All Fields)) AND ("critical illness"(MeSH Terms) OR ("critical"(All Fields) AND "illness"(All Fields)) OR "critical illness"(All Fields) OR ("critically"(All Fields) AND "ill"(All Fields)) OR "critically ill"(All Fields)) AND ("adult"(MeSH Terms) OR "adult"(All Fields) OR "adults"(All Fields)) AND ("randomized controlled trial"(Publication Type) OR "randomized controlled trials as topic"(MeSH Terms) OR "randomized controlled trial"(All Fields) OR "randomised controlled trial"(All Fields)); ("Plasma-lyte 148"(Supplementary Concept) OR "Plasma-lyte 148"(All Fields) OR "plasma lyte 148"(All Fields)) AND versus(All Fields) AND ("sodium chloride"(MeSH Terms) OR ("sodium"(All Fields) AND "chloride"(All Fields)) OR "sodium chloride"(All Fields) OR "saline"(All Fields)) AND ("intensive care units"(MeSH Terms) OR ("intensive"(All Fields) AND "care"(All Fields) AND "units"(All Fields)) OR "intensive care units"(All Fields) OR ("intensive"(All Fields) AND "care"(All Fields) AND "unit"(All Fields)) OR "intensive care unit"(All Fields))

We used the following search terms in the Cochrane search strategy: "Balanced Crystalloids versus Normal Saline" in Title, Abstract, Keywords AND "Critically Ill Adutls", "Intensive Care Unit", "Mortality", "Acute Kidney Injury", "Renal Replacement Therapy", and "Randomized Controlled Trial" in Search All Text in the Trials.