ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults — A Systematic Review with Meta-Analysis

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Abstract

BACKGROUND The comparative efficacy and safety of balanced crystalloid solutions and saline for fluid therapy in critically ill adults remain uncertain.

METHODS We systematically reviewed randomized clinical trials (RCTs) comparing the use of balanced crystalloids with saline in critically ill adults. The primary outcome was 90-day mortality after pooling data from low-risk-of-bias trials using a random-effects model. We also performed a Bayesian meta-analysis to describe the primary treatment effect in probability terms. Secondary outcomes included the incidence of acute kidney injury (AKI), new treatment with renal replacement therapy (RRT), and ventilator-free and vasopressor-free days to day 28.

RESULTS We identified 13 RCTs, comprising 35,884 participants. From six trials (34,450 participants) with a low risk of bias, the risk ratio (RR) for 90-day mortality with balanced crystalloids versus saline was 0.96 (95% confidence interval [CI], 0.91 to 1.01; $I^2 = 12.1\%$); using vague priors, the posterior probability that balanced crystalloids reduce mortality was 89.5%. The RRs of developing AKI and of being treated with RRT with balanced crystalloids versus saline were 0.96 (95% CI, 0.89 to 1.02) and 0.95 (95% CI, 0.81 to 1.11), respectively. Ventilator-free days (mean difference, 0.18 days; 95% CI, −0.45 to 0.81) and vasopressor-free days (mean difference, 0.19 days; 95% CI, −0.14 to 0.51) were similar between groups.

CONCLUSIONS The estimated effect of using balanced crystalloids versus saline in critically ill adults ranges from a 9% relative reduction to a 1% relative increase in the risk of death, with a high probability that the average effect of using balanced crystalloids is to reduce mortality. (PROSPERO number, CRD42021243399.)

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Introduction

Reports of intravenous fluids being used to treat critically ill adults date back almost 200 years,[1] and these fluids remain one of the most commonly used treatments in such patients.[2,3] Most fluids used for intravenous therapy were approved and licensed for use on the basis of small trials in relatively few patients, which used short-term physiological changes or absence of acute toxicity as outcome measures.[4,5] In the absence of robust data, controversy over the choice of intravenous fluid continues,[6] with the choice of fluid driven by local practice rather than by evidence.[2] Over the past 20 years, large investigator-initiated trials have convincingly demonstrated that albumin offers no benefit over crystalloids in a heterogeneous population of critically ill adults[7] and may be harmful in patients with traumatic brain injury.[8] In addition, hydroxyethyl starch, the most commonly used synthetic colloid, has been shown to increase the risk of acute kidney injury[9,10] and, in some populations, the risk of death.[9] These findings have resulted in greater use of crystalloid solutions in intensive care units (ICUs).[3] At the same time, concerns have arisen about the potential toxicity of 0.9% sodium chloride (saline), which causes hyperchloremic metabolic acidosis when given rapidly or in large volumes[11,12] and may increase the risk of acute kidney injury.[13] This has led to the increased use of balanced salt solutions — crystalloid solutions with a chloride concentration close to that of plasma — even in the absence of convincing evidence that their use improves patient-centered outcomes.[3] A large cluster crossover trial conducted in the ICUs of a single medical center in the United States provided evidence in support of using balanced solutions rather than saline,[14] although the evidence provided was not considered definitive.[15] Recently, two large trials have reported their results.[16,17] Therefore, to provide an updated summary of the available evidence, we conducted a systematic review and meta-analysis to address the following clinical question: In critically ill adults, does the use of balanced crystalloid solutions compared with saline reduce mortality and/or the occurrence of acute kidney injury?

Methods

We conducted this systematic review according to a prespecified protocol registered at the international prospective register of systematic reviews (PROSPERO), which was also published before data analysis.[18] The full protocol is included in the Supplementary Appendix. This review is reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 checklist.[19]

ELIGIBILITY CRITERIA

Randomized clinical trials (RCTs) and cluster RCTs were eligible for inclusion if they recruited critically ill adult patients, including those recruited in an ICU or in an emergency or operating room and then transferred to an ICU; these trials compared fluid therapy with balanced crystalloid solutions (e.g., Plasma-Lyte, Hartmann's solution, and Ringer's lactate) with saline. Fluid therapy was defined as fluid given intravenously for resuscitation (expansion of intravascular volume) and/or maintenance (fluid given to provide normal daily water and electrolyte requirements). Nonrandomized trials, trials of patients who were not critically ill, and trials in which there was concern about scientific misconduct were excluded.[20] There was no language restriction, and we included all reports, including studies reported only as abstracts.

SEARCH STRATEGY

We systematically searched Medline, EMBASE, and five clinical trials registries (listed in the Supplementary Appendix) from inception until the end of February 2021, using the OVID interface for eligible trials. The search strategy included multiple medical subject heading terms and keywords for balanced crystalloid solutions and normal saline, as well as sensitive search filters to identify RCTs, crossover trials, and cluster RCTs.[21,22]

We limited the search to human and adult studies with no restrictions on language, publication date, or publication status. Furthermore, we searched the reference lists of relevant primary research and review articles, trial registries, and published abstracts. Finally, we contacted recognized experts in critical care fluid therapy. The full details of the electronic search strategy are available in the Supplementary Appendix.

STUDY SELECTION

With the aid of a reference management system,[23] a minimum of two investigators independently screened all retrieved references for inclusion on the basis of the study title and abstract. A minimum of two reviewers retrieved and reviewed for inclusion the full text of articles deemed possibly eligible. We resolved disagreement during the

review process by discussion with a third reviewer and by consensus.

DATA COLLECTION

Two investigators, not affiliated with the included studies, independently extracted data from each included trial using a standardized data collection form. We extracted all available data as outlined in the protocol, including characteristics of the included studies, design (RCT or cluster RCT), details of the population enrolled (including demographic data, illness severity, and indices of organ dysfunction at baseline), details of the study interventions (including specific balanced crystalloid solution compared with saline), and study fluid use (for resuscitation, maintenance, or both). Data specified in the protocol that were not available from the trial reports were requested from the corresponding authors of the included studies. For the Plasma-Lyte 148 versus Saline (PLUS)[17] study and the Sodium Chloride or Plasma-Lyte 148 Evaluation in Severe Diabetic Keto-Acidosis (SCOPE-DKA)[24] study, we had access to the study data before publication. We resolved discrepancies in the data extracted by the two reviewers by discussion or, if necessary, by adjudication by a third reviewer.

RISK OF BIAS ASSESSMENT

Two investigators with no affiliation with the included trials independently assessed the risk of bias for each of the included trials using the Cochrane Risk of Bias Tool version 2, which incorporates domains specific to cluster and crossover RCTs.[25] Disagreements were resolved by discussion with a third reviewer and by consensus. Clarifications regarding details of the methods of included studies were sought from corresponding authors when these were not clear in published protocols, statistical analysis plans, or trial reports. We adjudicated risk of bias as low only if all domains were assessed as low risk of bias.

MISSING DATA

We attempted to obtain missing data from the study authors. We did not impute missing data.

OUTCOMES

The primary outcome was all-cause mortality at 90 days in low-risk-of-bias trials. For trials in which this was not available, we used reported mortality at the point nearest to (before or after) 90 days.

Where available, we collected data regarding the following secondary outcomes: the proportion of patients with acute kidney injury as defined in the original trial, mortality at the longest interval, the proportion of participants newly treated with renal replacement therapy, ventilator- and vasopressor-free days to day 28, quality of life, and functional outcomes.

SUBGROUP ANALYSES

We assessed the heterogeneity of treatment effect on the primary outcome as follows. For trial-level subgroups, we assessed trials with a low risk of bias versus those with some concerns or a high risk of bias, cluster RCT versus individual patient RCT, and type of balanced crystalloid (Plasma-Lyte 148 compared with other/mixed balanced crystalloids). We could not perform the planned analysis on the basis of study fluid use for maintenance fluids only compared with all fluids, because no included trials used study fluids for maintenance only. Instead, we conducted an analysis comparing trials that used study fluid only for resuscitation with those in which it was used for all fluids. There were insufficient numbers of included studies to meaningfully perform the planned between-group, patient-level subgroup analyses.[26]

For patient-level subpopulations where data were available, we report the primary outcome by fluid type within subgroups of patients with sepsis, trauma, and traumatic brain injury and patients admitted to the ICU after cardiac surgery. There were insufficient data to report effects in patients with diabetic ketoacidosis.

DATA SYNTHESIS

The primary analysis was performed with the Hartung-Knapp-Sidik-Jonkman random-effects model.[27] To evaluate the robustness of the estimates according to different estimates of the between-study variance, we also fitted a DerSimonian Laird random-effects model.

Because some of the included trials are cluster RCTs, we took account of clustering by adjusting the raw data for the design effect by using the effective sample size approach — that is, the original sample size is divided by the design effect, which is $1 + ($average cluster size $- 1) \times$ intracluster correlation coefficient.[28]

We also conducted a Bayesian meta-analysis to further explore the robustness of the results and to calculate the probability of treatment effect lying on a particular range

of value (i.e., risk ratios [RRs] < 1). Analyses were performed using vague (unit information prior for the log-RR and half-normal with scale 0.5 for τ) and semi-informative (a more precise log-RR distribution centered at 0 and a log-normal prior based on the distribution suggested for mortality and pharmacologic comparisons) priors.[29]

We present results as RRs for binary outcomes and mean differences for continuous outcomes. We also present pooled effect sizes and 95% confidence intervals (CIs) and credible intervals (CrIs; for the Bayesian meta-analysis). We also report the prediction intervals. Quantitative heterogeneity was assessed by performing a formal test of homogeneity and evaluating the proportion of total variability attributable to heterogeneity rather than to sampling error (I^2). Small-study effects and publication bias were assessed by the regression-based Egger test and visual evaluation of contour-enhanced funnel plots. All outcomes (except trial-level subpopulations) are reported for low-risk-of-bias trials.

All statistical analyses were performed using Stata 17 software (StataCorp LLC, College Station, TX) and the package bayesmeta in R.[30]

GRADING THE QUALITY OF EVIDENCE

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the overall quality of evidence for each outcome measure.[31]

Results

We retrieved a total of 1779 records plus three unpublished studies. Figure 1 shows the results of the search and reasons we excluded studies. We included 11 studies[14,17,24,32–39] and two conference abstracts,[40,41] for a total of 35,884 trial participants. The characteristics of the included studies are shown in Table 1.

We adjudicated six studies with 34,450 participants as having a low risk of bias in all domains, and we rated all other studies as non low risk of bias (either some concern or high risk of bias in at least one domain [Fig. S1 and Table S1 in the Supplementary Appendix]).

PRIMARY OUTCOME

Using the Hartung-Knapp-Sidik-Jonkman method, the pooled estimated RR for 90-day mortality (or closest

time point) for balanced crystalloid solutions compared with saline in the six studies with low risk of bias was 0.96 (95% CI, 0.91 to 1.01; $I^2 = 12.1\%$) as shown in Figure 2 and Figures S2 and S3. There was no evidence of publication or small study bias on visual inspection of the funnel plot or by the Egger test (Fig. S4). The effect of fluid allocation on mortality was similar when all studies were pooled regardless of risk of bias (Fig. S5), with an estimated RR of 0.93 (95% CI, 0.76 to 1.15; $I^2 = 88.4\%$). When accounting for cluster effects, the estimated RR was 0.96 (95% CI, 0.92 to 1.02) (Fig. S6). When the studies were pooled using the DerSimonian Laird method, the estimated RR was 0.96 (95% CI, 0.92 to 1.01; $I^2 = 0\%$) (Table 2). The result of the Bayesian meta-analysis for the low-risk-of-bias studies using vague priors was consistent with the primary analysis, with a posterior probability of the RR of 0.96 (95% CrI, 0.88 to 1.04), with an 89.5% probability that balanced crystalloid solutions were associated with lower mortality compared with saline (Fig. S7 and Fig. S8). Sensitivity analysis using Bayesian methods with vague and semi-informative priors and including all trials produced similar results (Fig. S9 and Fig. S10).

SECONDARY OUTCOMES

In the trials adjudicated as low risk of bias, treatment with balanced solutions compared with saline was associated with a RR of developing acute kidney injury of 0.96 (95% CI, 0.89 to 1.02) and a RR of being treated with renal replacement therapy of 0.95 (95% CI, 0.81 to 1.11). Results including all trials were similar (Table 2; Figs. S11–S14). There was no significant difference in ventilator-free days (pooled estimated mean difference, 0.18 days; 95% CI, −0.45 to 0.81) or vasopressor-free days (pooled estimated mean difference, 0.19 days; 95% CI, −0.13 to 0.51) between those assigned to balanced solutions versus saline (Table 2; Figs. S15 and S16). There were no data to report longer-term mortality (beyond 90 days) in the included studies. There were no data available to provide a pooled estimate of quality of life and functional outcomes.

SUBGROUP ANALYSIS

The primary outcome of 90-day mortality was assessed in trial-level (Table 2) and in patient-level subgroups of low-risk-of-bias trials (Table 2; Figs. S17–S21). There was no evidence that the pooled estimate for mortality was different for cluster RCTs versus individual patient RCTs (test of group difference P=0.80) (Table 2) or for trials
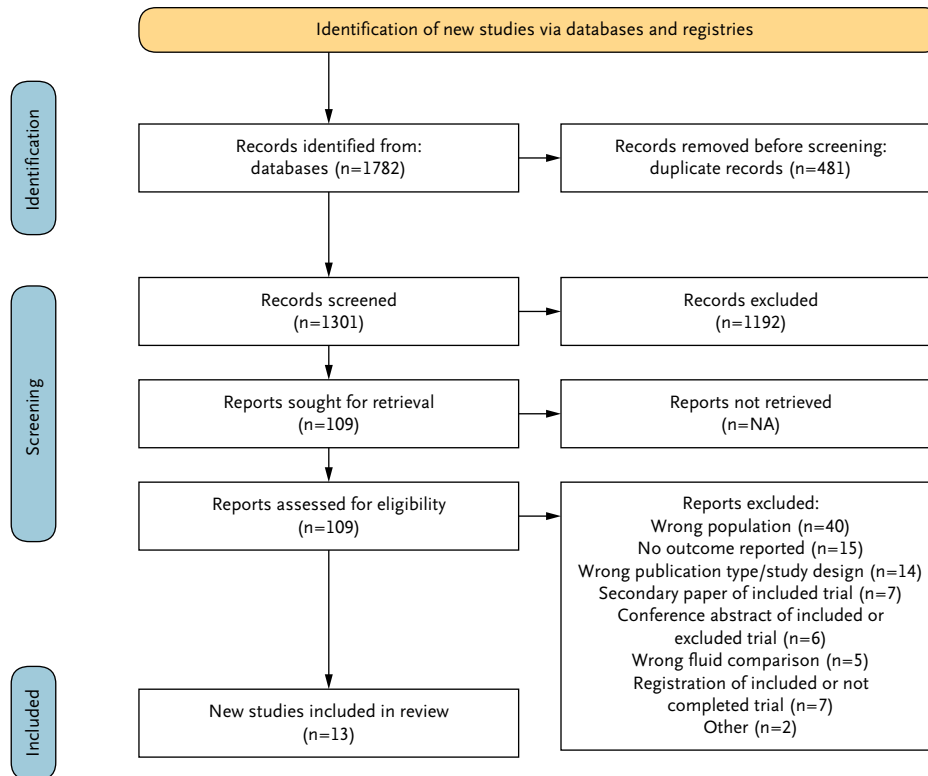
Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flow Diagram of Results of Search and Reasons for Exclusion of Studies.

Designed using Haddaway NR, Pritchard CC, McGuinness LA. PRISMA2020: R package and ShinyApp for producing PRISMA 2020 compliant flow diagrams. 2021. Zenodo available (https://www.eshackathon.org/software/PRISMA2020.html).

using Plasma-Lyte 148 compared with other or mixed balanced crystalloids (P=0.74) (Table 2). There were no trials in which the fluid intervention was given only as maintenance fluids. In three trials, the assigned fluid therapy was given only for resuscitation, compared with eight studies in which the assigned fluid was used for all indications with no evidence that the pooled estimate of the RR was different (P=0.53) (Table 2).

For the patient-level subgroups, the included trials provided insufficient data to perform the planned between-group analyses. Five trials adjudicated as low risk of bias reported outcomes of 6754 participants with sepsis at baseline. The pooled estimate of the RR for mortality for those assigned to receive balanced crystalloid solution compared with saline was 0.93 (95% CI, 0.86 to 1.01; $I^2=22.3\%$) (Table 2; Fig. S17). Including the one high-risk-of-bias trial that reported outcomes in patients with sepsis produced a similar result (RR, 0.93; 95% CI, 0.85 to 1.01; $I^2=19.3\%$) (Fig. S18).

Three trials, all adjudicated low risk of bias, reported outcomes of 1896 participants with traumatic brain injury at baseline. Trial participants assigned to balanced crystalloid solutions compared with saline had an estimated pooled RR of 1.26 (95% CI, 0.98 to 1.60; $I^2=20.2\%$) (Table 2; Fig. S19).

Four trials, all adjudicated as low risk of bias, reported outcomes of 3863 participants with trauma at baseline. The pooled estimate of the RR for mortality for those assigned to receive balanced crystalloid solution compared with saline was 0.99 (95% CI, 0.70 to 1.39; $I^2=16.5\%$) (Table 2; Fig. S20).

Three trials, all adjudicated as low risk of bias, reported outcomes of 2420 participants who were admitted to the ICU after cardiac surgery. The pooled estimate of the RR for mortality for those assigned to receive balanced crystalloid solution compared with saline was 1.13 (95% CI, 0.76 to 1.69; $I^2=7.6\%$) (Table 2; Fig. S21).

Table 1. Characteristics of Included Trials.*

Reference	Year	Design	Country	Centers/ ICUs (n)	Participants (n)	Population/ Setting	Balance Fluid Used†	Fluid Administration (Resuscitation, All Fluid Therapy)	Median Volume		Duration	Primary Outcome	Mortality Time Point Closest to 90 d
									BSS	Saline			
Waters et al.[36]	2001	Blinded RCT	USA	1	66	Cardiac ICU	Lactated Ringer's	Intraoperative (all fluids)	6,871	7,000	Surgery duration	Change in base excess	In hospital
Young et al.[37]	2014	Blinded RCT	USA	1	65	Trauma ICU	Plasma-Lyte A	Resuscitation	10,300‡	9,000‡	24 hr	Change in base excess in the first 24 hr	In hospital (censored at 30 d)
Young et al.[38]	2015	Blinded cxRCT	NZ	4	2,278	Mixed ICUs	Plasma-Lyte 148	All fluids	2,000	2,000	ICU, up to 90 d	Kidney replacement therapy	In hospital (censored at 90 d)
Verma et al.[35]	2016	Blinded RCT	Australia	3	70	Mixed ICU	Plasma-Lyte 148	All fluids	2,933	3,443	ICU stay	Maximum base excess in the first 4 d	In hospital
Semler et al.[34]	2017	Unblinded cxRCT	USA	1	974	Medical ICU	Lactated Ringer's/ Plasma-Lyte 148	All fluids	1,617	1,424	30 d	MAKE30§	In hospital (within 30 d)
Ratanarat et al.[41]	2017	Unblinded RCT	Thailand	NR	181	Shock (ED/ ICU)	Sterofundin	Resuscitation	11,158	11,189	72 hr	Acute kidney injury up to 7 d	NR
Choosakul et al.[32]	2018	Unblinded RCT	Thailand	1	47	Acute pancreatitis (ED/ICU)	Lactated Ringer's	Resuscitation	4,929‡	5,347‡	ED	Systemic inflammatory response syndrome criteria reduction	30 d
Kunupakan et al.[40]	2018	RCT¶	Thailand	NR	59	Sepsis	Ringer's acetate	Resuscitation	100	1,000	72 hr	Median difference of uNGAL levels on day 3	NR
Semler et al.[14]	2018	Unblinded cxRCT	USA	1/5 ICUs‖	15,802	Mixed specialty ICUs	Lactated Ringer's/ Plasma-Lyte 148	All fluids	1,000	1,020	30 d	MAKE30§	In hospital (30 d)
Golla et al.[33]	2020	Unblinded RCT	India	1	160	Sepsis (ED/ ICU)	Lactated Ringer's	Resuscitation	35,000	3,500	NR	Incidence of hyperchloremia at 24 hr and during hospital stay	30 d
Ramanan et al.[24]	2021	Unblinded cxRCT	Australia	7	93	Diabetic ketoacidosis (ED/ICU)	Plasma-Lyte 148	All fluids	6,798‡	6,574‡	ED and ICU, up to 48 hr	Diabetic ketoacidosis resolution	In hospital
Zampieri et al.[39]	2021	Blinded RCT	Brazil	75	10,520	Mixed medical and surgical ICUs	Plasma-Lyte 148	All fluids	2,900**	2,900**	ICU, up to 90 d	90-d mortality	90 d
Finfer et al.[17]	2022	Blinded RCT	ANZ	53	5,037	Mixed medical and surgical ICUs	Plasma-Lyte 148	All fluids	3,900	3,700	ICU, up to 90 d	90-d mortality	90 d

* ANZ denotes Australia and New Zealand, BSS indicates balanced salt solution, cxRCT indicates cluster crossover randomized clinical trial, ED indicates emergency department, ICU indicates intensive care unit, NR = not reported, NZ indicates New Zealand, RCT indicates randomized clinical trial, and uNGAL indicates urinary neutrophil gelatinase-associated lipocalin.

† The pH of the listed fluids are as follows: lactated Ringer's, 6.5; Plasma-Lyte A, 7.4; Plasma-Lyte 148, 7.4; Sterofundin, 5.1 to 5.9; Ringer's acetate, 4.6 to 5.4.

‡ Indicates mean value is reported.

§ MAKE30: indicates Major Adverse Kidney Events within 30 days, a composite end point of mortality, treatment with kidney replacement therapy, and/ or doubling creatinine.

¶ This RCT did not report if the study fluid was blinded or not.

‖ Indicates the number of centers and number of ICUs differed.

** Indicates median volume infused up to day 3.

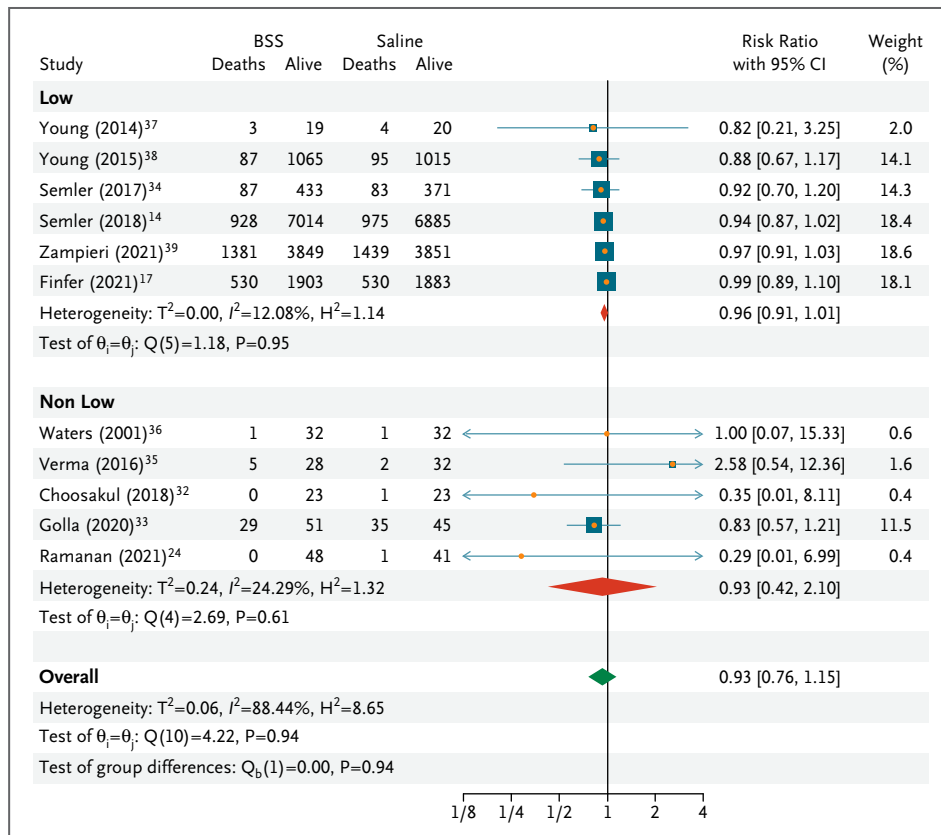| Study	BSS Deaths	BSS Alive	Saline Deaths	Saline Alive		Risk Ratio with 95% CI	Weight (%)
Low							
Young (2014)[37]	3	19	4	20		0.82 [0.21, 3.25]	2.0
Young (2015)[38]	87	1065	95	1015		0.88 [0.67, 1.17]	14.1
Semler (2017)[34]	87	433	83	371		0.92 [0.70, 1.20]	14.3
Semler (2018)[14]	928	7014	975	6885		0.94 [0.87, 1.02]	18.4
Zampieri (2021)[39]	1381	3849	1439	3851		0.97 [0.91, 1.03]	18.6
Finfer (2021)[17]	530	1903	530	1883		0.99 [0.89, 1.10]	18.1
Heterogeneity: T^2=0.00, I^2=12.08%, H^2=1.14						0.96 [0.91, 1.01]	
Test of $\theta_i=\theta_j$: Q(5)=1.18, P=0.95							
Non Low							
Waters (2001)[36]	1	32	1	32		1.00 [0.07, 15.33]	0.6
Verma (2016)[35]	5	28	2	32		2.58 [0.54, 12.36]	1.6
Choosakul (2018)[32]	0	23	1	23		0.35 [0.01, 8.11]	0.4
Golla (2020)[33]	29	51	35	45		0.83 [0.57, 1.21]	11.5
Ramanan (2021)[24]	0	48	1	41		0.29 [0.01, 6.99]	0.4
Heterogeneity: T^2=0.24, I^2=24.29%, H^2=1.32						0.93 [0.42, 2.10]	
Test of $\theta_i=\theta_j$: Q(4)=2.69, P=0.61							
Overall						0.93 [0.76, 1.15]	
Heterogeneity: T^2=0.06, I^2=88.44%, H^2=8.65							
Test of $\theta_i=\theta_j$: Q(10)=4.22, P=0.94							
Test of group differences: Q_b(1)=0.00, P=0.94							

1/8 1/4 1/2 1 2 4

Figure 2. Effect of Balanced Crystalloids Compared with Saline on 90-Day Mortality in Critically Ill Patients by Risk of Bias.

Low indicates low risk of bias. Non low trials were rated as having either some concern or high risk of bias. Saline is 0.9% sodium chloride. Red dots denote point estimates, blue boxes are CIs, blue lines are prediction intervals, red diamonds denote CIs of the pooled estimate, and the green diamond represents the pooled estimate CIs of all trials. BSS denotes balanced salt solutions and CI confidence interval.

SUMMARY OF FINDINGS AND RECOMMENDATIONS

The quality of evidence as assessed by the GRADE criteria for 90-day mortality, incidence of acute kidney injury, and treatment with renal replacement therapy was high, moderate, and low, respectively (Table 3).

Discussion

In this systematic review and meta-analysis, the estimated effect of using balanced crystalloids versus saline for fluid therapy in critically ill adults ranged from a 9% relative reduction to a 1% relative increase in risk of death by 90 days or the nearest reported time point. This result was stable when other random-effects meta-analytic methods were used and after the effect of clustering was taken into account. The estimate of effect was stable when including only low-risk-of-bias trials or all trials regardless of risk of

bias; including trials at higher risk of bias produced wider CIs, hence suggesting greater uncertainty around the result. Our Bayesian meta-analysis indicated a high probability that using balanced salt solutions reduces the risk of death.

Our estimate of the effect of balanced crystalloids versus saline on mortality in patients with sepsis is consistent with a 14% relative reduction to a 1% relative increase in risk of death. In contrast, our estimate for patients with traumatic brain injury is consistent with a 2% relative reduction but a 60% relative increase in risk of death, suggesting that the average treatment effect may obscure important and contrasting subgroup effects.

STRENGTHS

To our knowledge, our review provides the most up-to-date evidence of the effect of balanced salt solutions

Table 2. Outcomes for Low Risk of Bias Trials Except for Trial-Level Subgroups.

Outcome	Trials (n)	Participants (n)	τ^2	I^2 (%)	Effect measure (RR* or MD§)	95% CI	β
Low-risk-of-bias trials							
Primary outcome: 90-d mortality	6	34,450	0.001	12.1	0.96	0.91 to 1.01	
Sensitivity analysis for the primary outcome							
DerSimonian Laird	6	34,450	<0.001	0	0.96	0.92 to 1.01	
Bayesian meta-analysis	6	34,450	1.03	NA	0.96	0.88 to 1.04‡	
Accounting for cluster effect	6	34,450	0.00	8.18	0.96	0.92 to 1.02	
Secondary outcomes							
Treated with renal replacement therapy	5	33,554	0.02	59.5	0.95	0.81 to 1.11	
Incidence of acute kidney injury	5	25,224	0.00	8.6	0.96	0.89 to 1.02	
Ventilator-free days (to day 28)	5	32,191	0.32	79.5	0.18§	−0.45 to 0.81	
Vasopressor-free days (to day 28)	3	21,622	0.02	24.1	0.19§	−0.13 to 0.51	
Patient-level subgroup analysis for the primary outcome							
Sepsis	5	6,754	0.001	22.3	0.93	0.86 to 1.01	
Traumatic brain injury	3	1,896	0.01	20.2	1.26	0.98 to 1.60	
Trauma	4	3,863	0.03	16.5	0.99	0.70 to 1.39	
Cardiac surgery	3	2,420	0.01	7.6	1.13	0.76 to 1.69	
All trials: trial-level subgroup analysis for the primary outcome							
Cluster crossover	4	19,128	0.04	68.4	0.91	0.71 to 1.17	0.80
Individual patient randomly assigned	7	15,752	0.07	87.1	0.96	0.70 to 1.31	
Plasma-Lyte 148	5	17,785	0.16	95.8	0.99	0.64 to 1.54	0.74
Other/mixed balanced fluids	6	17,095	0.01	23.4	0.91	0.77 to 1.08	
All fluids	8	34,627	0.07	92.2	0.96	0.76 to 1.20	0.53
Resuscitation fluids only	3	253	0.02	4.6	0.81	0.52 to 1.27	

* RR denotes risk ratio, § MD denotes mean difference
NA indicates not applicable.
‡ Indicates values are for credible interval.

compared with saline on important patient-centered outcomes. It includes substantial new data and a large number of outcome events not available to previous meta-analyses,[42,43] thus providing greater precision around estimates of treatment effects.

The methodologic strengths of this review include a focused research question with a defined population, intervention, and comparator. We developed, registered, and prepublished a protocol.[18] Three reviewers independently selected the studies we included, with a fourth reviewer adjudicating any differences. We contacted authors of published conference abstracts and registered clinical trials that met our inclusion criteria to find additional results to include in this review. We used the latest tool to assess risk of bias including domains for cluster and crossover trials. Two assessors, who were not investigators in any of the included trials, independently assessed the risk of bias, with all discrepancies adjudicated by a third

independent reviewer. We assessed six of the included trials as low risk of bias; these trials were the largest trials contributing the majority of the data to the meta-analyses. We performed both frequentist and Bayesian analyses to provide comprehensive assessments of treatment effects to guide clinical practice.

LIMITATIONS

Limitations of this review relate mainly to the characteristics of the included trials, which reported outcomes at different time points and used different definitions for outcome measures such as acute kidney injury. Many trials either did not include or did not report outcomes in subgroups of interest, meaning we had limited power to detect clinically important subgroup effects. We planned to report data on longer-term quality of life and functional outcomes, but none of the included trials have reported these data as yet.

Table 3. Summary of Findings and Certainty of Evidence: Balanced Crystalloids Compared with 0.9% Saline for Critically Ill Adults Requiring Fluid Therapy.*

Outcome	Anticipated Absolute Effect (95% CI)†		Relative Effect, RR (95% CI)	No. of Participants	No. of RCTs	Certainty of the Evidence (GRADE)‡	Comments
	Risk with Balanced Crystalloids	Risk with Saline					
All-cause mortality at 90 d	211 per 1000 (205 to 218)	223 per 1000 (216 to 230)	0.96 (0.91 to 1.01)	34,450	6	⊕⊕⊕⊕ (high)	
Incidence of acute kidney injury	140 per 1000 (134 to 147)	147 per 1000 (141 to 154)	0.96 (0.89 to 1.02)	25,224	5	⊕⊕⊕○ (moderate)§	Downgraded one level because of inconsistency in the definition of acute kidney injury
New treatment with renal replacement therapy	60 per 1000 (56 to 64)	64 per 1000 (60 to 68)	0.99 (0.78 to 1.29)	33,554	5	⊕⊕○○ (low)§,¶	Downgraded two levels because of imprecision, evidenced by the wide confidence limits and for inconsistency as evidenced by the heterogeneity ($I^2=84.2\%$)
Ventilator-free days to day 28	22 (19 to 25)	21 (19 to 24)	0.18 (−0.45 to 0.81)‖	32,191	5	⊕⊕⊕○ (moderate)§	Downgraded one level because of a degree of inconsistency evidenced by heterogeneity ($I^2=79.5\%$)
Vasopressor-free days to day 28	23 (18 to 29)	23 (18 to 28)	0.19 (−0.13 to 0.51)‖	21,622	3	⊕⊕⊕⊕ (high)	
Health-related quality of life	NR	NR	NR	NR	NR	NA	NA

* Patient or population: critically ill adults; setting: intensive care unit or high dependency unit; intervention: balanced crystalloids; and comparison: 0.9% saline. GRADE: Grading of Recommendations, Assessment, Development and Evaluations, CI denotes confidence interval, RCT indicates randomized clinical trial, RR denotes risk ratio, NA indicates not applicable, and NR indicates not reported.

† The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). 95% CIs were calculated with the Wilson score method with continuity correction. Mortality at longest follow-up was not assessed because no trials reported mortality beyond the primary outcome of 90 days. All outcomes are reported on the basis of low-risk-of-bias trials.

‡ GRADE indicates Grading of Recommendations Assessment, Development and Evaluation Working Group grades of evidence which are as follows. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

§ Indicates downgraded for serious inconsistency.

¶ Indicates downgraded for serious imprecision.

‖ Indicates mean difference is presented.

Additionally, there are aspects of trials of fluid therapy management in critically ill patients, such as the type and volume of fluid given before random assignment and the volume of fluid given after random assignment, that may contribute to heterogeneity of outcomes, which cannot be assessed in a trial-level meta-analysis.

IMPLICATIONS

Because fluids are administered to almost all critically ill patients, even a small difference in mortality or other relevant outcomes may result in important clinical and economic effects at the population level. Moreover, given that the fluids we evaluated are widely available and clinicians regularly need to choose between them, an unbiased assessment of the probability that one type of fluid is preferable to another may have important implications for practice. Our Bayesian analysis suggests there is a high probability that the average treatment effect of using balanced crystalloids in a heterogeneous population of critically ill patients is to reduce mortality. However, taking a frequentist approach, which leads to a dichotomized yes

or no conclusion on the basis of CIs that do or do not include unity (P<0.05 or not), would lead to a conclusion that balanced solutions do not reduce mortality. This approach does not recognize the uncertainty regarding the possible extent and direction of the true treatment effect, which is indicated by the CIs. As a result, the inferences drawn from our study will depend on an individual's preference for a frequentist or Bayesian approach to interpreting the data. In addition, clinical decision-making might reasonably be influenced by the baseline risk of death of individual patients or populations being treated, as well as other factors, including compatibility with other intravenous fluids and medications[44] and fluid acquisition costs, which vary among countries.[45]

UNANSWERED QUESTIONS AND FUTURE RESEARCH

Our review provides estimates of an average treatment effect in a heterogeneous population of critically ill adults. These results do not rule out the possibility of differential treatment effects in subpopulations, and the prediction intervals around the estimates of treatment effects do not rule out clinically important treatment effects in future trials in different clinical settings. Better understanding of such effects could be gained from a patient-level meta-analysis and from additional trials in more selected populations.

Conclusions

Our systematic review and meta-analysis of currently existing data indicates that the estimated effect of using balanced crystalloids rather than saline for intravenous fluid therapy in a heterogeneous population of critically ill adults ranges from a 9% relative reduction to a 1% relative increase in death by 90 days. Overall, there is a high probability that the average treatment effect of using balanced crystalloids is to reduce mortality.

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Disclosures

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