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REVIEW ARTICLE

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Acetate- versus lactate-buffered crystalloid solutions: A systematic review with meta-analysis and trial sequential analysis

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Abstract

Objective: There is a widespread use of buffered crystalloid solutions in clinical practice. However, guidelines do not distinguish between specific types of buffered solutions and clinical equipoise exists. We aimed to assess the desirable and undesirable effects of acetate- versus lactate-buffered solutions in hospitalised patients.

Methods: We conducted a systematic review with meta-analysis and trial sequential analysis of randomised clinical trials assessing the use of acetate- versus lactate-buffered solutions for intravenous administration in hospitalised adults and children. The primary outcome was all-cause short-term mortality. We adhered to our published protocol, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, the Cochrane Handbook and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology.

Results: We included five RCTs enrolling 390 patients. We found no statistically significant difference in short-term mortality (random effects, risk ratio [RR] 0.29; 95% confidence interval [CI] 0.06–1.51, $p = .14$, $I^2 = 0\%$) or hospital length of stay (LOS) (random effects, mean difference [MD]−1.31, 95% CI −3.66 to 1.05, $p = .28$, $I^2 = 0\%$) between acetate- versus lactate-buffered solutions. The quality of evidence was very low. Data regarding intensive care unit LOS were reported by three trials and duration of vasopressor treatment by one trial; none of these data allowed for pooling in meta-analyses. No trials reported data on long-term mortality, health-related quality of life, adverse events, duration of mechanical ventilation or renal replacement therapy.

Conclusion: In this systematic review, we found very low quantity and quality of evidence on the use of acetate- versus lactate-buffered solutions in hospitalised patients.

KEYWORDS
acetate, crystalloid, fluid therapy, lactate

Editorial Comment

Buffered crystalloid solutions are increasingly used in balanced fluid therapy. This include acetated and lactated solutions. It is uncertain if these solutions differ in adverse events or are harmful for patients. The effects of these solutions could potentially influence a significant number of patients worldwide, particularly those with critical illness who are treated at the ICU. The review points towards a significant need for further and large scale trials investigating benefit and harm of these everyday treatments.

1 | BACKGROUND

Intravenous (IV) fluid therapy is widely used in daily clinical practice.[1] Several different types of fluid, intended for various purposes, are available. Among these are isotonic crystalloid solutions comprising normal saline and different buffered solutions.

The use of isotonic crystalloids has increased over the last decade.[2–4] However, clinical practice guidelines increasingly recommend buffered solutions over normal saline as the latter has been associated with unwarranted effects such as hyperchloremic acidosis and possibly increased risk of acute kidney injury (AKI).[5–8]

The buffered solutions (often referred to as "balanced" or "physiologic" solutions) were originally developed to resemble the composition of extracellular fluid closer than normal saline. However, these solutions continue to differ from the composition of plasma. In comparison, they are relatively hypotonic and contain alternative anions, such as acetate or lactate, as a substitute to the naturally occurring buffer bicarbonate.[9,10]

Harm has been suggested from excessive administration of acetate- and lactate-buffered crystalloid solutions. Acetated solutions might cause cardiotoxicity[11–13] while lactated solutions may result in hyperlactatemia and possibly be inappropriate for patients with impaired liver function.[14,15] Importantly, these concerns are based on findings from experimental- and observational studies as well as theoretical conceptions. Hence, the clinical implications remain unknown.

The effects of these alternative buffers in clinical practice are poorly described, and the adverse events differ between the solutions.[16] Current clinical practice guidelines do not distinguish between the different types of buffered solutions depending on their buffering anion.[6,7] As buffered crystalloid solutions have varying compositions, considering them as a single class of fluid could potentially cause for misinterpretation of different effects between the different solutions thus underlining the importance of this research question. Assessment of interventions used in everyday clinical practice is highly important, as several commonly used interventions have been shown to be at best ineffective, but also harmful for some interventions.[17] This highlights the need to scrutinise routine clinical interventions used by many patients, including the use of buffered crystalloid solutions.

Accordingly, we aimed to summarise and assess the benefits and harms of acetate- versus lactate-buffered crystalloid solutions in hospitalised patients. We hypothesised that the available evidence on the use of acetate- versus lactate buffered solutions in hospitalised patients would be sparse.

2 | METHODS

We conducted this systematic review according to a prespecified published protocol,[18] and the protocol was registered in the International Prospective Register of Systematic Reviews PROSPERO(CRD42020199743) prior to publication.

We followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions;[19] the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[20] (Electronic supplementary material [ESM], PRISMA checklist); and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[21]

2.1 | Types of studies

We included randomised clinical trials (RCTs) assessing the use of acetate- versus lactate-buffered crystalloid solutions in hospitalised patients. We imposed no restrictions regarding language, blinding, publication source or -status. We excluded quasi-randomised trials, individual crossover trials and observational studies.[18]

2.2 | Types of participants

We included trials conducted in adults or children admitted to hospital for any reason. We excluded trials in animals and healthy subjects.[18]

2.3 | Types of interventions

We included RCTs assessing IV administration of any primarily acetate-buffered solution (i.e., Ringer's Acetate, Plasmalyte™, Normosol™, Kabilyte™, Sterofundin™, Ionosteril™ etc.) versus any primarily lactate-buffered solution (i.e., Ringer's Lactate or Hartmann's solution). Interventions were considered eligible irrespective of timing, dosing, and duration of treatment and multiple intervention- and control groups were permitted. Trials in which patients were randomised to other supplemental IV fluids in both the intervention and control group were permitted, if identical solutions were administered in both arms.[18]

2.4 | Types of outcome measures

2.4.1 | Primary outcome measure

The primary outcome was all-cause short-term mortality ≤90 days, including in-Intensive Care Unit (ICU) and in-hospital mortality.

2.4.2 | Secondary outcome measures

Secondary outcomes included;

(1) All-cause long-term mortality >90 days, (2) adverse events (as defined by the original trials) at the longest follow-up, (3) health-related quality of life (any continuous scale used in the included trials) at the longest follow-up, (4) hospital length of stay (LOS), (5) ICU LOS, (6) days alive without/duration of mechanical ventilation (if both were available, we report the outcome for which most data exist), (7) days alive without/duration of renal replacement therapy (if both were available, we report the outcome for which most data exist), (8) days alive without/duration of vasopressor/inotropic treatment (if both were available, we report the outcome for which most data exist).

2.4.3 | Search methods for identification of studies

We systematically searched MEDLINE (PubMed interface, 1966 onwards), Embase (OVID interface, 1947 onwards), The Cochrane Central Register of Controlled Trials (2018, Issue 10) and Epistemonikos. In addition, we searched databases of ongoing trials from clinical trial registries. We manually searched reference lists of relevant trials and systematic reviews. All searches were conducted from inception to December 6, 2021, when the last search was performed. The full search strategy is provided in the ESM 2.

2.5 | Data collection and analysis

2.5.1 | Selection of studies

Two authors (K.L.E. and P.S.) independently screened articles for inclusion based on titles and abstracts. Potentially eligible articles were independently evaluated in full text by two authors (K.L.E. and P.S.). Disagreements were resolved by discussion with a third senior author (M.H.M. or A.P.).

2.5.2 | Data extraction and management

Two authors independently extracted data using a standardised data extraction form in duplicate (ESM Table 3.1–3.4). Extracted data items included trial characteristics (year of publication, country and number of trial sites), characteristics of trial settings (i.e. medical-, surgical- or emergency department [ED] or intensive care unit) population (inclusion- and exclusion criteria), intervention/comparator (type of fluid, indication for use, amount of fluid infused, fluid administration protocol and duration of intervention) and data on the predefined outcome measures.

If prespecified data were not available authors were contacted for further data. Authors of all five included trials were contacted[22–26] of which one author of two trials replied and provided additional data.[24,25] Disagreements were resolved by discussion with a third senior author (M.H.M. or A.P.).

2.5.3 | Risk of bias

Two authors independently assessed the risk of bias of the included trials using the Risk Of Bias tool 2 (ROB2) from the Cochrane Collaboration.[19,27] For each included trial, we assessed the following bias domains: (1) bias arising from the randomisation process, (2) bias because of deviations from intended interventions, (3) bias because of missing outcome data, (4) bias in measurement of the outcome and (5) bias in selection of the reported result.[27] Trials were adjudicated as having an either overall low risk of bias, some concerns or high risk of bias for individual outcome measures. The overall risk of bias assessment for each specific outcome was based on the worst risk of bias assessment in any of the prespecified domains, that is, if one or more domains were judged as being high risk of bias, we classified the trial as having overall high risk of bias for the particular outcome, if one or more domains were judged as some concerns of bias we judged the trial as having overall some concerns of bias, and if all trials were judged as low risk of bias we judged the trial as having overall low risk of bias.[27] Disagreements were resolved by discussion with a third senior author (M.H.M. or A.P.).

2.6 | Data synthesis

2.6.1 | Measures of treatment effect

We calculated relative risks (RRs) with corresponding 95% confidence intervals (CIs) for dichotomous outcomes and mean difference (MD) with corresponding standard deviation (SD) for continuous outcomes. If trials reported alternative measures for continues outcomes, for example, median and inter quartile range (IQR), authors were contacted for additional data. If authors failed to reply, the respective continuous outcome data were not pooled, and we reported median and IQR descriptively. Intention-to-treat (ITT) analyses were reported if available. We reported the most conservative treatment effect estimate using either fixed or random effects models.[18]

The primary result is based on data from all available trials regardless of the risk of bias evaluation.

2.6.2 | Data analysis

We used R version 4.0.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) with the *meta* package to conduct the

conventional meta- and subgroup analyses. We used Trial Sequential Analysis (TSA) version 0.9.5.10 b (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, available from http://www.ctu.dk/tsa) to conduct the TSA.

2.6.3 | Assessment of heterogeneity

We assessed statistical heterogeneity by inspecting forest plots and by using the inconsistency (I2) and diversity (D2) statistics[28,29] with thresholds as suggested by the Cochrane handbook.[19] We used both random-effects models (assuming that the true intervention effects in the included trials are not identical but follow normal distribution) and fixed-effect models (assuming that the true effect of the intervention in both direction and magnitude is fixed across included trials) across outcomes, and we reported the most conservative estimates (highest *p*-value) for cautiousness.[30,31] We addressed potential statistical heterogeneity in the pre-planned subgroup analyses.[18]

2.6.4 | Assessment of small trial bias

Fewer than 10 trials were included, thus we did not assess the risk of small trial bias.[18]

2.6.5 | Subgroup analyses

We planned to conduct five subgroup analyses; (1) trials with an overall high versus low risk of bias, (2) trials conducted in ICU versus non-ICU patients, (3) trials conducted in surgical versus non-surgical settings, (4) trials in children versus adults (as defined by the original trial) and (5) trials assessing administration of higher versus lower volumes of buffered crystalloid solution (defined as < versus > the median of administered fluid volumes across trials).[18] We used the chi-squared test to assess the statistical heterogeneity across patient subgroups considering a *p*-value of .10 as statistically significant.

2.6.6 | Sensitivity analysis

We applied empirical continuity correction if zero event trials were included in our meta-analyses.[32] We did not conduct sensitivity analysis with best-to-worst-case and worst-to-best-case scenarios, as no trials reported loss to follow-up.[18]

2.6.7 | Assessment of risk of random errors

We used trial sequential analysis (TSA) to assess the risk of random errors because of sparse data and multiple significance testing. In brief, TSA estimates the required information size needed to detect or reject an a priori pre-specified realistic intervention effect in a meta-analysis and widens the CIs (TSA adjusted CI) in cases where data are too sparse to draw conclusions.[29,33,34] Moreover, we used TSA to test for futility by applying futility boundaries. We applied trial sequential monitoring boundaries according to an a priori 15% RR difference for dichotomous outcomes and an a priori MD of 1 day for continuous outcomes, a family-wise error rate equal to an alpha of 5% for all outcomes, a beta of 10% (power of 90%), and a control event proportion as per the control arm of the included trials.[30,31,35] According to our statistical analysis plan, we considered $p < .05$ as statistically significant for the primary- and secondary outcomes, given that we had data available for analysis for only one of eight secondary outcomes.[18] As per our protocol we do not present TSA details or plots if, according to the TSA, <5% of the diversity-adjusted required information size was accrued.[18]

2.6.8 | Assessment of the overall quality of evidence

Two authors (K.L.E. and P.S.) independently assessed the quality of evidence for all outcomes using the GRADE methodology.[21] The overall quality of evidence was rated high, moderate, low or very low based on evaluations of risks of bias, inconsistency, indirectness, imprecision and publication bias across studies.

3 | RESULTS

We screened 7475 records, assessed 50 trials in full-text and included five trials ($n = 392$ randomised patients) in the systematic review.[22–26] 26 A total of four trials ($n = 288$) could be included in the meta-analyses.[22–25] In addition, we identified three on-going trials.[36–38] The main reasons for excluding trials were wrong study design and wrong outcome measures (Figure 1—PRISMA flowchart).

3.1 | Characteristics of trials

The included trials were published from 2011 through 2020. Four were single-centre trials[22–24,26] and one was a multicentre trial;[25] the largest trial included 150 patients.[23] Four trials included patients in a planned surgical setting,[23–26] and one trial included burn patients in a specialised ICU.[22] All trials were published in English. Further trial characteristics are provided in Table 1.

3.2 | Description of the intervention

The type of intervention/comparator and fluid administration protocols varied between trials. In three trials the administration of trial fluid was limited to the perioperative period,[23,25,26] one trial assessed the use of crystalloid solutions intraoperatively as CABG priming fluid[24] and one trial assessed the use of buffered crystalloid solutions as resuscitation fluid in critically ill burn patients for 5 days following

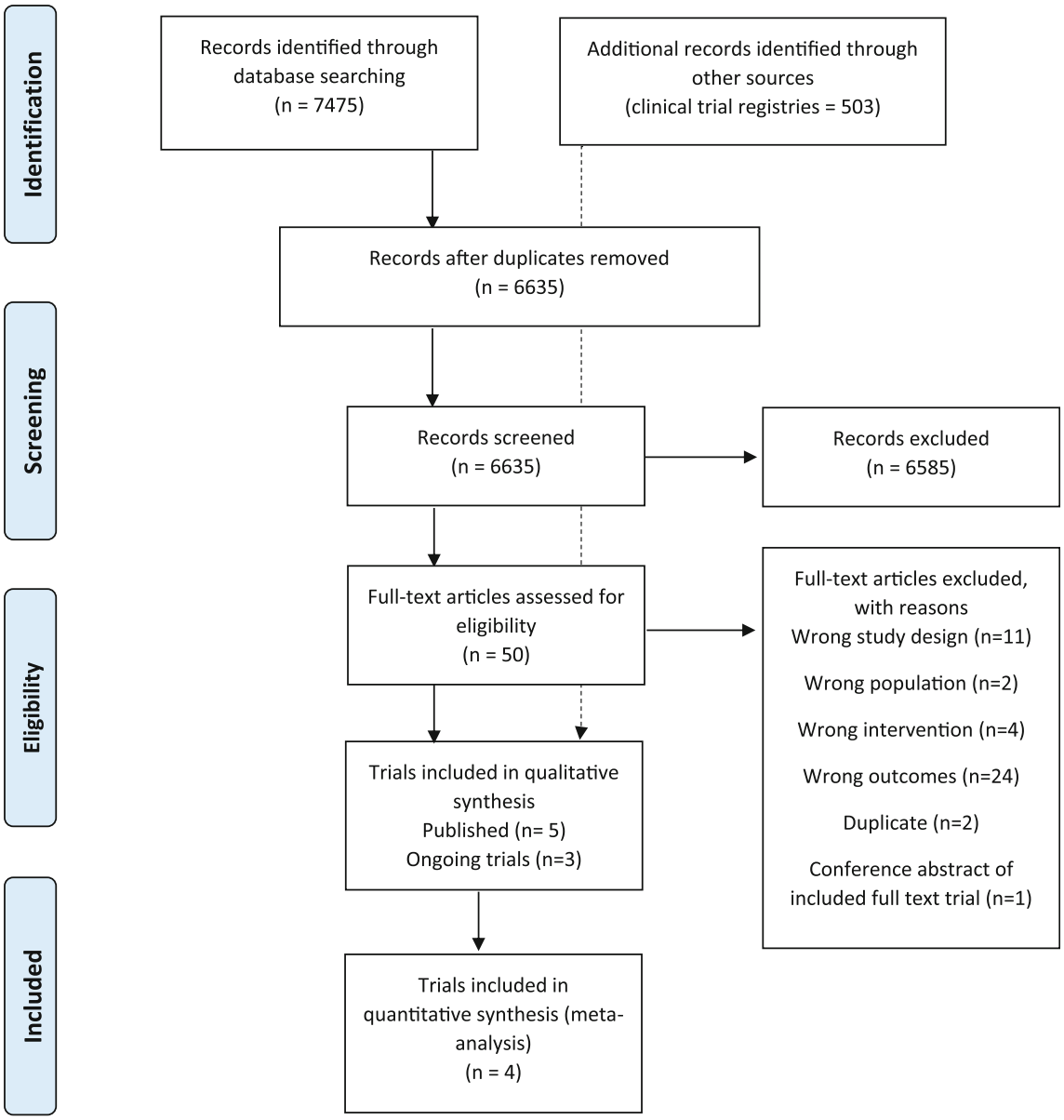

FIGURE 1 PRISMA flow chart

admission to the ICU.[22] Total volumes of trial fluids infused varied from a minimum of 2.2 L per patient[25] to a maximum of 19.6 L within the study period.[22] The most studied solutions were Plasma-Lyte versus Ringer's lactate. Full details on fluid consumption within the trials are available in the ESM Table 4.

3.3 | Risk of bias

All included trials were adjudicated as having overall 'low' or 'some concerns' risk of bias for all available outcomes (Figures 2.1–2.4). The main reason for concerns were risk of bias because of deviations from the intended interventions and selection of reported results. Further details on the risk of bias assessment are presented in ESM Table 6.1–6.5.

3.4 | Primary outcome

3.4.1 | All-cause short-term mortality ≤90 days

Four trials (n = 286) reported data on short-term mortality.[22–25] We found no statistically significant difference in short-term mortality between patients receiving acetate- versus lactate buffered crystalloid solutions (random effects, RR 0.29; 95% CI 0.06–1.51, p = .14, I^2 = 0%) (Figure 3). TSA could not be performed as <1% of the required information size of 39,835 patients had been accrued. Subgroup analyses were consistent with the primary estimate (ESM Table 7.3). The quality of evidence was very low because of inconsistency and imprecision (Table 2).

TABLE 1 Trial characteristics

Study/year	Country	Single/ multicentre trial (no. of sites)	No. of patients	Clinical setting	Population	Exclusion criteria	Acetate-buffered solution (no. randomised)	Lactate-buffered solution (no. randomised)	Patient-important outcomes
Chaussard et al/2020[22]	France	Single	28	Tertiary Burn ICU	Patients >18 years, with burns (>30% TBSA)	Pregnancy, refusal to participate and do not resuscitate orders	Plasmalyte ($n = 14$)	Ringers Lactate ($n = 14$)	28-day mortality and ICU length of stay
Pfortmüller et al/2019[23]	Switzerland	Single	150	Surgery and ICU	Patients 18–80 years, undergoing elective open cardiac surgery	<18 years or >80 years. Pre-existing impaired cardiac or renal function, anaemia, chronic inflammatory- or liver disease. Long term steroid medication, active infection, emergency- or redo surgery and isolated CABG surgery. Planned use of minimal extracorporeal circuits, early extubation protocols or restrictions to full therapy	Ringers Acetate ($n = 75$)	Ringers Lactate ($n = 75$)	In-hospital mortality, hospital length of stay, ICU length of stay and duration of inotropic /vasopressor treatment
Weinberg et al/2018[24]	Australia	Single	50	Surgery	Adults undergoing elective primary CABG or valve surgery	Requirement of Custodial® HTK cardioplegia solution, pregnancy, abnormal plasma bicarbonate concentration, hypercapnic respiratory failure, chronic renal- or liver disease, diabetes, anaemia or morbid obesity	Plasmalyte-148 ($n = 25$)	Hartmann's solution ($n = 25$)	In-hospital mortality, hospital length of stay and ICU length of stay
Weinberg et al/2015[25]	Australia	Multi (4)	60	Surgery	Adult patients, undergoing elective open major liver resection	<18 years, laparoscopic or minimally invasive surgery, hepatic- or renal impairment, preoperative coagulopathy, and ASA score 4 or 5	Plasmalyte-148 ($n = 30$)	Hartmann's solution ($n = 30$)	30-day mortality, hospital length of stay and ICU length of stay
Shin et al/2011[26]	Korea	Single	104	Surgery	Living liver donors undergoing scheduled right hepatectomy	>40 years, emergency donors, left hepatectomy, had >30% fatty change	Plasmalyte ($n = 52$)	Ringers Lactate ($n = 52$)	Post-operative hospital stay
Semler MW/Ongoing trial (NCT03537898)	USA	Single	Expected 2093	Medical ICU	Patients ≥18 years admitted to the Medical ICU	Prisoners	Normosol	Ringers Lactate	30-day in-hospital mortality, renal replacement therapy-free days,

(Continues)

TABLE 1 (Continued)

Study/year	Country	Single/ multicentre trial (no. of sites)	No. of patients	Clinical setting	Population	Exclusion criteria	Acetate-buffered solution (no. randomised)	Lactate-buffered solution (no. randomised)	Patient-important outcomes
									vasopressor-free days, ventilator-free days, intensive care unit-free days
Weiss S/Ongoing trial (NCT04102371)	USA	Multi (30+)	Expected 8800	Paediatric dept. and ED's receiving paediatric patients	Patients >6 months to <18 years with suspected sepsis who received <40 ml/kg IV/IO total crystalloid fluid prior to randomisation	Hyperkalaemia, hypercalcemia, hepatic- or renal impairment, metabolic disorder, impending brain herniation, pregnancy or known allergy to study fluids. prisoners	Plasmalyte	Ringers Lactate	All-cause 90-day mortality
Raman S/Ongoing trial[38]	Australia	Single	Expected 480	Paediatric ICU	Patients age from birth to <16 years admitted to PICU within the last 24 h and received IVFT for ≤4 h in PICU. All fluids must have been administered in PICU. Patients sodium level >130 mmol/L	Age >16 years, received IVFT for >4 h in PICU or admitted for cardiac condition or chronic kidney disease. Patients with Traumatic brain injury, burns, post-liver transplant, post-renal transplant, ketoacidosis, major electrolyte abnormalities or oncologic patients in need of rehydration	Plasmalyte	Compound sodium lactate	Organ dysfunction free survival, PICU LOS, hospital LOS, PICU free survival and adverse event

Abbreviations: ASA, American Society of Anaesthesiology score; CABG, coronary artery bypass grafting; ED, emergency department; ICU, intensive care unit; IO, intraosseous; IV, intravenous; IVFT, intravenous fluid therapy; PICU, paediatric intensive care unit; TBSA, total burn surface area.

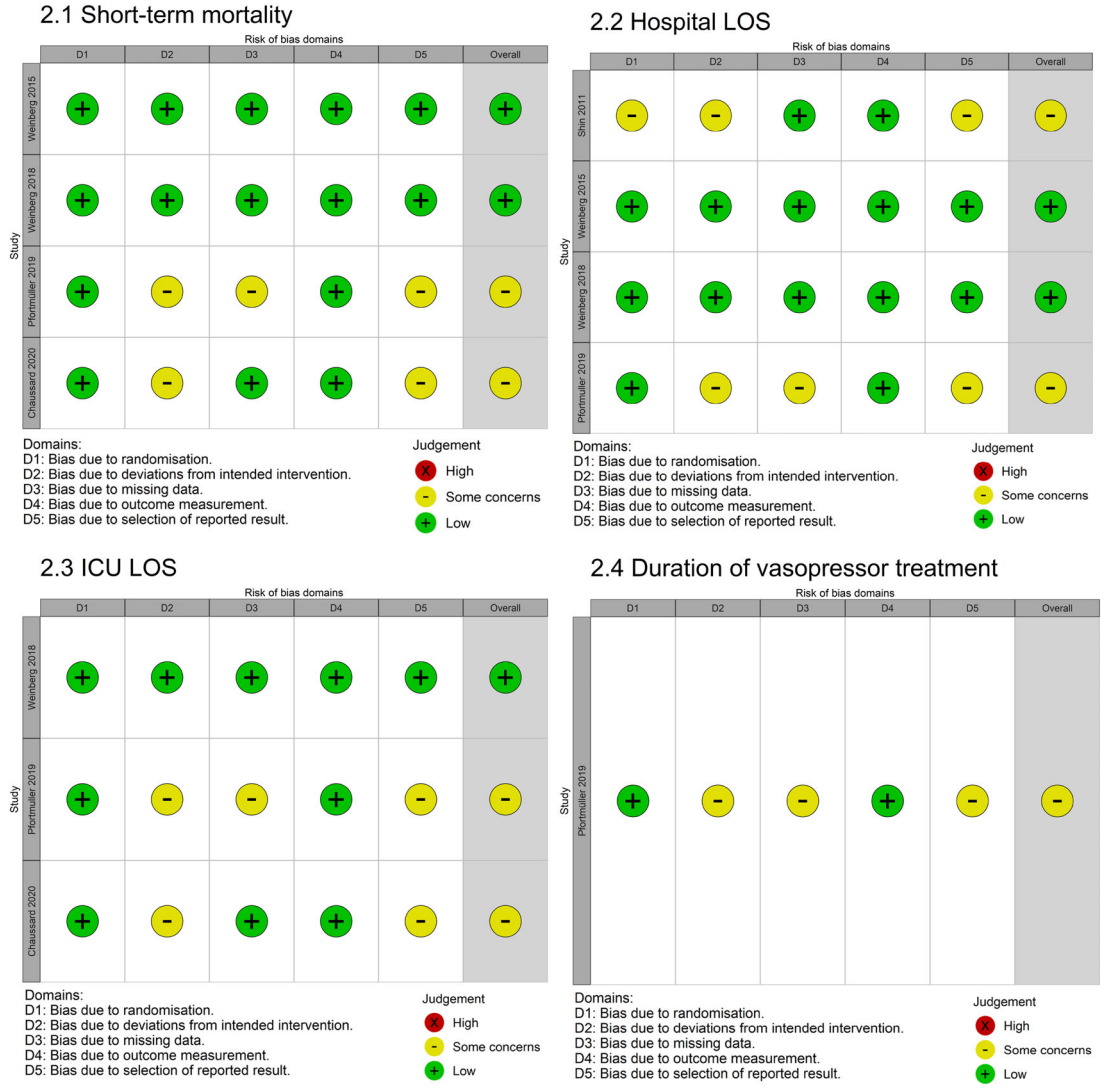

FIGURE 2 Risk of bias evaluation (ROB2) summary figures. Risk of bias was estimated for the following bias domains: (1) bias arising from the randomisation process, (2) bias because of deviations from intended interventions, (3) bias because of missing outcome data, (4) bias in measurement of the outcome and (5) bias in selection of the reported result

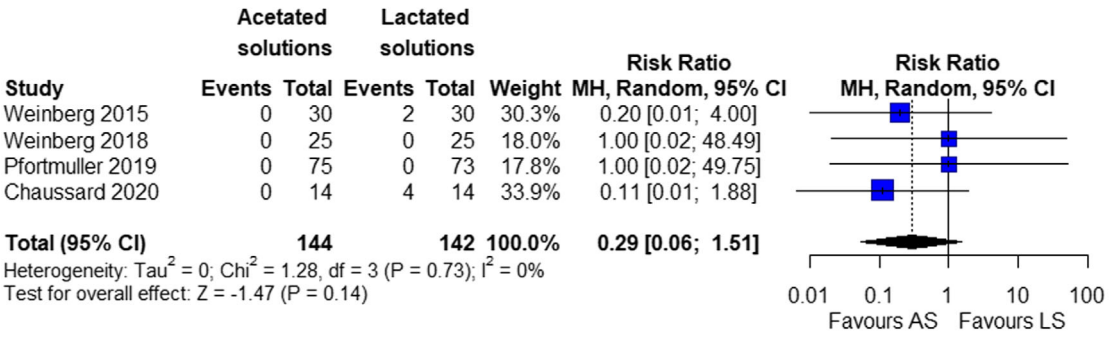

FIGURE 3 Forrest plot of primary outcome; all cause short-term mortality (random-effect model)

TABLE 2 Summary of findings table. Evaluation of the quality of evidence according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

Certainty assessment							№ of patients		Effect			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acetate-buffered crystalloid solutions	Lactate-buffered crystalloid solutions	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
All-cause short-term mortality ≤ 90 days												
4	Randomised trials	Not serious[a]	Serious[b,c]	Not serious	Very serious[d]	None	0/144 (0.0%)	6/142 (4.2%)	RR 0.15 (0.02 to 1.15)	36 fewer per 1.000 (from 41 fewer to 6 more)	⨁◯◯◯ Very low	Critical
All-cause long-term mortality >90 days—not reported												
–	–	–	–	–	–	–	–	–	–	–	–	Critical
Adverse events—not reported												
–	–	–	–	–	–	–	–	–	–	–	–	Critical
Health related quality of life (any scale)—not reported												
–	–	–	–	–	–	–	–	–	–	–	–	Critical
Hospital length of stay (assessed with: days)												
2	Randomised trials	Not serious[a]	Serious[c]	Not serious	Very serious[e]	None	182	180	–	MD 1.31 days lower (3.66 lower to 1.05 higher)	⨁◯◯◯ Very low	Important
ICU length of stay (assessed with days)												
3	Randomised trials	Not serious[a]	Serious[b,c]	Not serious	Very serious[d]	None	114	112	–	Not pooled	⨁◯◯◯ Very low	Important
Duration of mechanical ventilation (MV)—not reported												
–	–	–	–	–	–	–	–	–	–	–	–	Important
Duration of renal replacement therapy (RRT)—not reported												
–	–	–	–	–	–	–	–	–	–	–	–	Important
Duration of vasopressor/inotropics												
1	Randomised trials	Not serious[a]	Not serious	Not serious	Very serious[f]	None	75	73	–	0 (0–0)	⨁⨁◯◯ Low	Important

Abbreviations: CI, confidence interval; MD, mean difference; RR, risk ratio.

[a]Trials were judged as overall 'low' risk of bias or 'some concerns' (unclear risk of bias). Potential limitations are unlikely to lower confidence in the estimate of effect.

[b]Inconsistency downgraded because of differences in population.

[c]Inconsistency downgraded because of difference in interventions (e.g. one trial applied fluids as pump prime during CABG and one trial used fluids as resuscitation therapy in critically ill burn patients).

[d]TSA could not be performed because <5% of the required information size had been reached.

[e]TSA revealed that only 7% of the required information size had been accrued.

[f]Duration of vasopressor was reported by only 1 trial ($n = 150$).

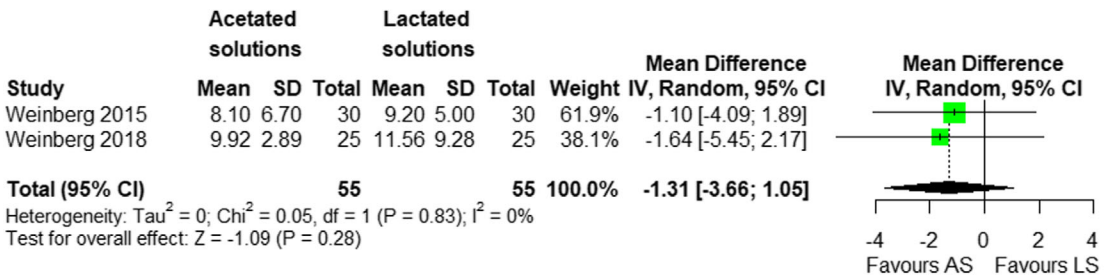

FIGURE 4 Forrest plot of hospital length of stay (random-effect model)

3.5 | Secondary outcome measures

3.5.1 | Hospital LOS

A total of four trials ($n = 362$) reported data on hospital LOS.[23–26] Data from two trials ($n = 110$) allowed for pooling in a meta-analysis.[24,25] We found no statistically significant difference in hospital LOS between the use of acetate versus lactate buffered crystalloid solutions (random effects, MD – 1.31, 95% CI −3.66 to 1.05, $p = .28$, $I^2 = 0\%$) (Figure 4). TSA found that 7% of the required information size of 1669 patients had been accrued (TSA-adjusted CI, −10.94 to 8.28) (ESM Figure 8). Data were not available for any subgroup analyses. The quality of evidence was very low because of inconsistency and imprecision (Table 2).

3.5.2 | ICU LOS

A total of three trials ($n = 226$) reported data on ICU LOS.[23,24,26] Data could not be pooled as only one trial provided results as mean (SD) (MD −1.30, 95% CI −3.66 to 1.06, $p = .28$)[24] while the remaining two trials reported LOS as median (IQR) (ESM Table 5.3).[23,26] All trials individually suggested no statistically significant difference in ICU LOS between patients receiving acetate- versus lactate-buffered solutions. The quality of evidence was very low because of inconsistency and imprecision (Table 2).

3.5.3 | Vasopressor/inotropic treatment

A total of one trial ($n = 150$) reported data on duration of vasopressor and inotropic treatment.[23] There was no statistically significant difference in duration of vasopressor/inotropics in between groups (ESM Table 5.4). The quality of evidence was low because of imprecision (Table 2).

3.5.4 | Other outcomes

No studies reported data on all-cause long-term mortality >90 days, adverse events, health-related quality of life, duration of/days alive without mechanical ventilation or duration of/days alive without renal replacement therapy.

3.6 | Subgroup analyses

We observed no interaction in the subgroup analyses of trials conducted in ICU versus non-ICU, trials conducted in medical- versus. surgical settings and trials administering lower versus higher volumes of trial fluid for the primary outcome short-term mortality (ESM Table 7.3). The remaining predefined subgroup analyses could not be carried out.

4 | DISCUSSION

In this systematic review of RCTs assessing the use of IV acetate- versus lactate-buffered crystalloid solutions in in adults or children admitted to hospital for any reason, we found very low quantity and quality of evidence supporting the decision on the type of buffered crystalloid solution used in hospitalised patients, that is, there was no firm evidence of benefit or harm.

4.1 | Summary of evidence

We found no statistically significant difference in all-cause short-term mortality, hospital- or ICU LOS between patients receiving IV acetate- versus lactate-buffered crystalloid solutions. TSA indicated a high risk of random errors and low quantity of data, and the overall quality of evidence was very low for most outcome measures. Thus, further high-quality trials are needed to establish firm evidence. Importantly, no trials reported data on "critical" secondary outcome measures, including the outcome adverse effects. Failure to report information on adverse effects hinders interpretation of overall effects.[39,40]

4.2 | Relation to current evidence

This review is the first systematic review of RCTs with meta-analysis and TSA comparing the use of buffered crystalloid solutions based on their buffering anion, that is, acetate- versus lactate-buffered solutions.

Several RCTs and reviews hereof have compared buffered solutions with normal saline without distinctively assessing the different types of buffered solutions.[41–46] A review by Curran et al.[47] assessed the use of different types of buffered crystalloid solutions based on

manufactural origin rather than on their buffering agent. They concluded that data on patient-important outcomes were too sparse and heterogeneous to allow for pooling, which is in line with our results. In addition, they suggested that, based on surrogate outcomes, Plasmalyte (a primarily acetate-buffered solution) may result in less metabolic abnormalities as compared with other buffered crystalloids. However, the clinical implications of these metabolic abnormalities are unknown.

The population investigated in our review primarily consisted of planned surgical patients. Hence, the possibility of heterogeneity of treatment effect cannot be dismissed, and the results may not be generalisable to all groups of hospitalised patients. This includes critically ill patients who might be more susceptible to the possible metabolic changes caused by different buffered solutions.[48]

Regarding the intervention, the amounts of fluid- and the duration of fluid therapy currently investigated, might not adequately represent daily clinical practice. It is likely, that patients in daily clinical practice receive larger amounts of fluid throughout hospitalisation, including inadvertently administered volumes as drug diluents or to preserve catheter patency.[49,50] A greater exposure to the intervention could potentially have a greater impact on patient-important outcomes. The importance of this is illustrated by a secondary analysis of the Isotonic Solutions and Major Adverse Renal Events Trial (SMART).[51] Among patients with sepsis, the effect of buffered crystalloids versus saline on mortality was greater among patients for whom fluid choice was controlled starting in the ED than in those commencing in the ICU.[51]

We exclusively evaluated patient-important outcome measures. Interestingly, a previous scoping review comparing acetate- versus lactate-buffered solutions regardless of study design or type of outcome found that less than 25% of studies reported patient-centered outcome measures.[16] Importantly, trials reporting surrogate outcome measures are more likely to produce falsely inflated estimates and are at increased risk of false-positive findings.[52,53]

Considering the vast use of buffered crystalloid solutions in clinical practice, the lack of data comparing their individual effects on patient-important outcomes is surprising. Importantly, we identified three on-going trials[36–38] investigating the effects of acetate- versus lactate-buffered solutions on patient-important outcome measures, including the large "BASE" pilot trial (Semler et al. expected $n = 2093$),[36] which will contribute markedly to the existing body of evidence.

4.3 | Implications for further research

Buffered crystalloid solutions are widely used in daily clinical practice likely because they are perceived as safe based on assumptions of their similarities to extracellular fluid. However, there is no firm evidence supporting their safety. Importantly, RCTs have previously shown harm from routine interventions in clinical practice, including that of fluid therapy.[17] Administration of colloid solutions have been shown to harm some patients groups as observed for albumin in patients with traumatic brain injury[54] and hydroxyethyl starch in patients with sepsis.[55] Clearly, we cannot treat our patients based on preconceived notions of the effectiveness and safety of a given intervention, as this can have potential serious ramifications for the individual patient.

It is possible that the use of fluids depending on their buffering anion, for example, acetate versus lactate does not significantly affect patient-centered outcomes. However, considering their vast use in clinical practice, even minor differences in the desirable or undesirable effects will affect many patients.

4.4 | Strengths and limitations

We published a protocol and statistical analysis plan prior to conducting the review. The review was planned and reported according to recommendations from the Cochrane collaboration, PRISMA statement and GRADE methodology. Furthermore, we used TSA to test the robustness of the meta-analysis and to estimate the required information size.[56] Other strengths include the comprehensive systematic search strategy, duplicate independent screening, data extraction and risk of bias assessment and assessment of patient-important outcome measures only.

Our review also holds limitations. First, the body of evidence consists of a limited number of small trials with overall some concern of bias for most outcomes, increasing the risk of falsely inflated effect estimates.[52] Second, the included trials were clinically heterogenous in terms of patient population, setting intervention/comparator (e.g. types of solution) and fluid administration protocol. Third, many of our predefined patient-important outcome measures were not reported, and the body of evidence describing these outcomes was limited resulting in clinical equipoise on the balance between benefits and harms. Fourth, we were not able to pool all available data as some trials reported continues outcomes only as median (range/IQR). Authors were contacted for additional data but only one replied. We refrained from calculating mean and SD using the reported median and IQR as suggested by the Cochrane Handbook,[19,57] as this approach assumes that the data are normally distributed. Furthermore, data conversion was not prespecified in the study protocol. Finally, we a priori considered a 15% RRD between groups clinically relevant. Consequently, smaller treatment effects cannot be ruled out.

5 | CONCLUSION

In this systematic review of RCTs assessing the use of IV acetate- versus lactate-buffered crystalloid solutions in adults and children admitted to hospital for any reason, we found very low quantity and quality of evidence supporting the decision on the type of buffered crystalloid solution, that is, there was no firm evidence for benefit or harm.

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AUTHOR CONTRIBUTIONS

KLE: study design, data extraction, data analysis and drafting of manuscript and approval of the final manuscript. AP: study design and critical revision of manuscript for important intellectual content and approval of the final manuscript. PS: data extraction and critical revision of manuscript for important intellectual content, and approval of the final manuscript. MHH: study design and critical revision of manuscript for important intellectual content and approval of the final manuscript.

CONFLICT OF INTEREST

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SUPPORTING INFORMATION

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