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Review Article

Lactate *versus* acetate buffered intravenous crystalloid solutions: a scoping review

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Abstract

Background: Buffered crystalloid solutions are increasingly recommended as first-line intravenous resuscitation fluids. However, guidelines do not distinguish between the different types of buffered solutions. The aim of this scoping review was to assess the evidence on the use of lactate- *vs* acetate-buffered crystalloid solutions and their potential benefits and harms.

Methods: We conducted this scoping review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews. We searched PubMed, Embase, Epistemonikos, and the Cochrane Library for studies assessing the effect of lactate- *vs* acetate-buffered crystalloid solutions on any outcome in adult hospitalised patients. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation approach.

Results: We included a total of 29 studies, 25 of which were clinical trials and four were observational studies. Most studies were conducted in surgical settings and indications for use were poorly described. The most commonly administered solutions were Ringer's lactate *vs* Ringer's acetate or Plasma-Lyte™. Outcomes included acid/base and electrolyte status; haemodynamic variables; and markers of renal and liver function, metabolism, and coagulation. Only a few studies reported patient-centred outcomes. Overall, the data provided no firm evidence for benefit or harm of either solution, and the quantity and quality of evidence were low.

Conclusions: The quantity and quality of evidence on the use of different buffered crystalloid intravenous solutions were low, data were derived primarily from surgical settings, and patient-important outcomes were rarely reported; thus, the balance between benefits and harms between these solutions is largely unknown.

Keywords: acetate; buffered solution; crystalloid; fluid therapy; intravenous fluid; lactate

Editor's key points

- Scoping reviews aim to identify and map available evidence on a specific topic.
- This scoping review assessed the body of evidence on the use, potential, and harms of lactate- *vs* acetate-buffered crystalloid intravenous solutions.
- Most studies were performed in an elective surgical setting, but without an indication for use.
- The overall quality of evidence supporting the use of lactate- *vs* acetate-buffered solutions was low, and there were almost no data in high-risk critically ill patients available.
- The balance between benefits and harms of lactate- *vs* acetate-buffered crystalloid solutions remains unknown.

intravenous fluid therapy is amongst the most commonly used interventions in everyday clinical practice.[1] intravenous fluids are used for fluid resuscitation, maintenance and replacement therapy, in medications, and as a part of parenteral nutrition.[2]

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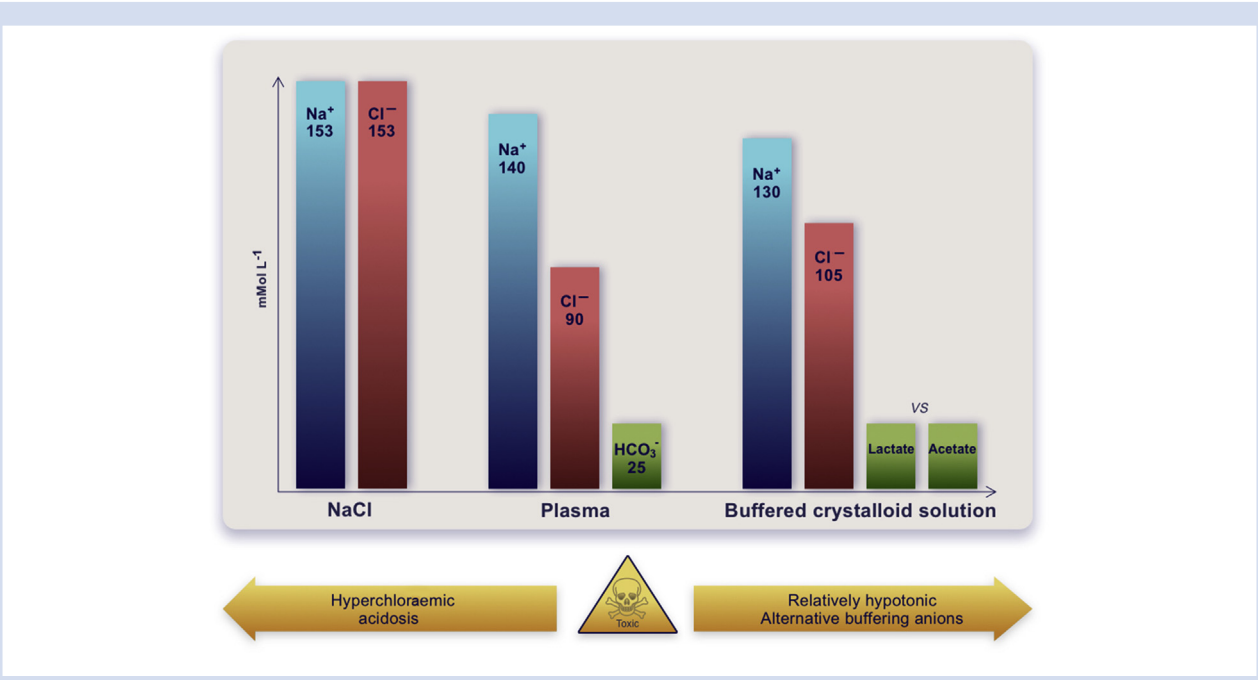

Fig 1. Compositions of isotonic crystalloid solutions compared with plasma and the potential adverse effects.

Several types of fluids are available, including crystalloids and colloids. The use of isotonic crystalloid fluid has increased over the last decade, and it is now the most frequently used type of i.v. fluid.[3–7]

Crystalloid solutions comprise isotonic saline and derivatives of the original Hartmann's and Ringer's solutions. With compositions that approximate extracellular fluid, the latter two have been labelled 'balanced', 'buffered', or 'physiological' crystalloid solutions, although none of the solutions are truly balanced or physiological with regard to electrolyte and buffer content.[8] Most buffered solutions have a lower sodium concentration than extracellular fluid and are therefore relatively hypotonic.[8,9] Furthermore, because of the instability of bicarbonate-containing solutions in soft plastic containers,[10] alternative anions, such as lactate and acetate and to a lesser extent gluconate and malate, are used as buffers in various combinations (Fig. 1).[8,9] The metabolism of these molecules varies; lactate and gluconate are metabolised to bicarbonate hepatically, whereas acetate is metabolised in several organs, but predominantly in peripheral skeletal muscle.[11] It is debated which anion is the better choice for the crystalloid solutions.[11]

Based on several recent RCTs comparing buffered solutions *vs* isotonic saline,[12–15] buffered solutions are increasingly recommended as first-line resuscitation fluids.[12,13,16] However, the choice between different buffered solutions appears to be difficult with limited data available to support the use of lactate- *vs* acetate-buffered solutions. Accordingly, we aimed to assess the body of evidence for the use of lactate- *vs* acetate-buffered crystalloid solutions and their potential desirable and undesirable effects in hospitalised patients.

Methods

This scoping review has been prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR).[17] The objective and methods of the review have been outlined in a pre-published protocol before initiation of this review.[18] There were no deviations from the protocol. The following research questions were posed:

(i) Which adult patient populations have received buffered solutions?
(ii) What are the indications for the use of buffered solutions?
(iii) Which buffered solutions do they receive?
(iv) Which outcomes have been assessed?
(v) What are the adverse effects and long-term effects of their use?

Eligibility criteria

We included all studies assessing the use of i.v. fluid therapy with buffered crystalloid solutions, for any reason, in adult hospitalised patients. The intervention and comparator of interest was any crystalloid solution primarily buffered with lactate *vs* any primarily acetate-buffered solution. We included trials with more than one intervention group. We included all study designs and gave priority to data from RCTs and systematic reviews. We included studies regardless of publication status, publication period, blinding, and language, and excluded trials on animals, children, and healthy subjects.

Search strategy

We systematically searched the Cochrane Library, MEDLINE, Embase, and Epistemonikos (Supplementary material B). In addition, we searched databases of ongoing trials, including ClinicalTrials.gov. The search strategy was pilot tested and refined before the final search was carried out. The latest search was performed on April 27, 2020. Furthermore, we hand

searched reference lists of relevant trials and other systematic reviews. During our search we identified several conference abstracts on the topic that were not presented as published trials. We contacted the authors in question to retrieve any potential unpublished articles/data not identified by our online search.

Study selection

The study selection process was completed using Covidence (www.covidence.org). Two authors (MMJ and KLE) independently reviewed all titles and abstracts identified in the literature search, and excluded trials that were deemed obviously irrelevant. The remaining trials were evaluated in full text. Trials in languages other than English or Scandinavian were translated independently by two authors (MMJ and KLE) using Google Translate. Disagreements were resolved with co-authors (MHM or AP).

Data extraction

Two authors (MMJ and KLE) independently extracted data from each included trial using a data extraction form. The extracted information included trial characteristics (trial design, year of publication, and country), patient characteristics (inclusion and exclusion criteria), type of intervention/comparator (including fluid administration protocol), and outcome measures. In cases of missing data, authors were contacted for additional information.

Outcome measures

We reported all available outcome measures provided in the included studies.

Assessment of risk of bias and quality of evidence

As per the pre-published protocol, we performed no detailed assessment of risk of bias in the individual studies. The quality of evidence for each outcome was assessed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[19] The quality of evidence was downgraded for risk of bias, inconsistency, indirectness, imprecision, and publication bias.[19] Accordingly, the quality of evidence was rated from 'high' to 'very low'. The quality assessment was performed independently by two authors (MMJ and KLE). Disagreements were resolved with co-authors (MHM or AP).

Data synthesis

We presented study characteristics, extracted data, and results descriptively, and grouped studies according to study design and year of publication to assess heterogeneity attributable to differences in design.

Results

We included a total of 29 studies: 25 clinical trials[20–44] and four observational studies[45–48]; four studies were only available in the form of conference abstracts[22,45–47] and three studies were ongoing at the time of this review with no retrievable data available.[42–44] The main reasons for full-text exclusion were wrong intervention or comparator (n=60), studies including no original data (n=38), and animal or paediatric populations (n=8) (Fig. 2).

Characteristics of studies

Details on study design, interventions, and comparators are presented in Supplementary material C. In brief, studies were published in English and Japanese, and were published between 1983 and 2020, with the exception of three ongoing clinical trials.[42–44] Of the 22 published clinical trials,[20–41] 13 were RCTs.[20–32] All four published observational studies were retrospective in design.[45–48]

Population investigated and indication for use

Seventeen clinical trials were conducted in a surgical setting with the intervention administered intraoperatively.[21,23–27,29–33,36–41] The remaining five clinical trials were conducted in burn units,[20,34,35] in an emergency department,[28] and in an ICU.[22] All four observational studies evaluated fluid therapy in a surgical setting.[45–48]

Indication for use was specified in 12 studies,[20–23,28,32–35,37,40,47] one of which compared the use of buffered solutions as pre-hydration before epidural anaesthesia,[32] and one specifically evaluated the use of solutions as replacement therapy,[47] one as maintenance therapy,[33] and five as predominantly resuscitation therapy.[20,22,28,34,35] Four studies evaluated the use of lactate- vs acetate-buffered solutions for cardiopulmonary bypass (CPB) pump prime.[21,23,37,40] The remaining 14 studies, all investigating intraoperative use of buffered solutions, did not provide details on the specific indication for the use of i.v. fluids.[24–27,29–31,36,38,39,41,45,46,48]

Type of fluid and administration protocol

The type of intervention/comparator and fluid administration protocols varied between studies (Supplementary material C). The acetate-buffered solutions that were investigated comprised Ringer's acetate, Plasma-Lyte™ (Baxter, Isolyte), Normosol™ (Hospira, Ionosteril), Kabilyte™ (Fresenius Kabi), Sterofundin™ (BRAUN), and Ionosteril™. The lactate-buffered solutions investigated included Ringer's lactate and Hartmann's solution. The most commonly studied solutions were Ringer's acetate or Plasma-Lyte vs Ringer's lactate.

Total volumes of study fluids infused varied from a minimum of 1.2 L per patient[32] to a maximum of 19.6 L Ringer's lactate (95% confidence interval [CI]: 14.7–25.5) vs 15.6 L Plasma-Lyte (95% CI: 12.2–26.6) within the study period.[20] This with the exception of one study that reported fluid volumes throughout hospital admission with median volumes on Day 28 coming to 34.1 (inter-quartile range [IQR]: 41.5) L of lactate-buffered fluid vs 42.9 (IQR: 35.5) L of acetate-buffered solution.[34] A total of 11 studies did not report total volumes of fluid infused.[28,30,31,33,37,39–41,45–47]

Outcome measures

Outcome measures varied between studies; for the sake of clarity, we categorised outcome measures as presented in Table 1. Results of the individual studies are presented in Supplementary material D and summarised as follows.

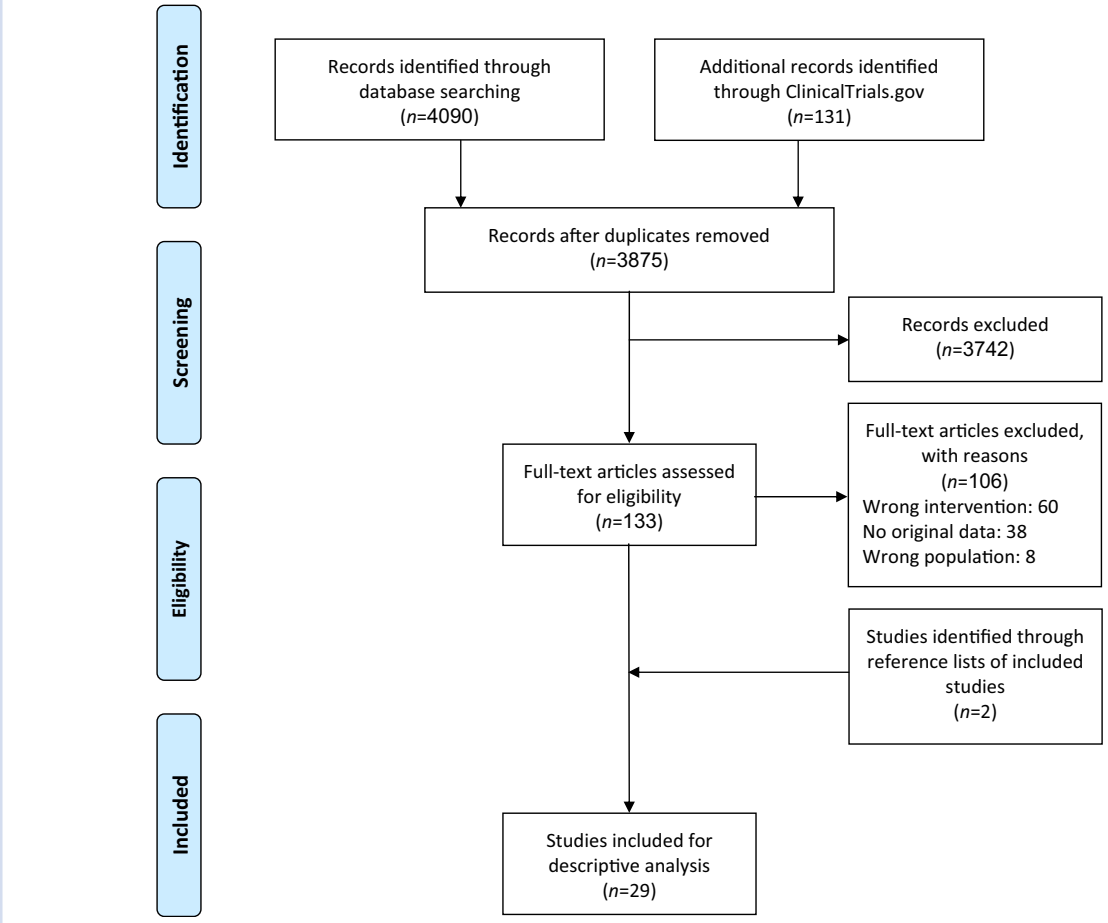

Fig 2. Preferred reporting items for systematic reviews and meta-analyses flow chart.[75]

Patient-centred outcome measures

Of the 29 included studies, a total of five clinical trials[20,21,23,26,34] and two observational studies[45,46] reported patient-centred outcome measures (e.g. mortality, length of stay [LOS] in ICU, return to ICU, days in ventilator, post-operative/infectious complications, and LOS in hospital). No studies reported the rate of adverse effects.

Regarding mortality, five studies found no statistically significant difference between groups,[20,21,23,26,34] whereas one study found an odds ratio with 95% CI for 90-day mortality of 0.96 (95% CI: 0.94–0.97) in the acetate- *vs* lactate-buffered group.[46]

Length of stay was addressed in six studies[20,21,23,26,34,45] with divergent results. Two studies found increased hospital LOS in the lactate- *vs* acetate-buffered group,[26,34] one found increased hospital LOS in the acetate-buffered group,[45] whilst the remaining two studies found no difference between groups.[21,23] No studies reported a statistically significant difference in ICU LOS between groups.[20,21,23,34]

A total of four studies addressed postoperative and infectious complications.[21,26,34,46] Overall, studies favoured acetate-buffered solutions, as one study reported fewer days in ventilator,[34] one found lower odds of respiratory failure,[46] one found lower occurrence of cardiac arrythmias,[21] and one found that the total number of complications was lower in the acetate- *vs* lactate-buffered group.[26]

The quality of evidence for patient-centred outcome measures was very low and downgraded because of risk of bias, inconsistency, and imprecision (Supplementary material E).

Non-patient-centred outcome measures

The non-patient-important outcome measures assessed by the included studies comprised acid/base and electrolyte status; haemodynamic variables; and markers of renal and liver function, metabolism, and coagulation (Table 1). Results within each category are summarised in Table 2.

Acid/base status was evaluated by 22 studies.[20–30,32–41,48] Overall, the most consistent result was an increased plasma lactate concentration in the lactate- *vs* acetate-buffered group.[21,23,24,26,27,29,30,34,36–39,41,48] The results of the remaining outcome measures depicting acid/base status were conflicting, with no clear effect of either solution. The overall quality of evidence was very low because of risk of bias, indirectness, and imprecision (Supplementary material E).

Haemodynamic parameters were assessed by 12 studies[20,21,24,25,30–32,36–38,40,48]; in eight studies, no significant differences were found in patients receiving acetate- *vs*

Table 1 Outcome measures by category. LOS, length of stay.

Category	Specific outcome measures within category
Patient-centred outcome measures	Hospital LOS; ICU LOS; postoperative/infectious complications; in-hospital mortality; and 28-, 30-, 60-, and 90-day mortality
Acid/base status	pH, base excess, hydrogen carbonate, lactate, acetate, gluconate, pyruvate, strong ion gap, and strong ion difference
Haemodynamics	HR, BP, MAP, central venous pressure, perfusion pressure, cardiac output, left ventricular ejection fraction, systemic vascular resistance, need of inopressor/vasopressor, and core and peripheral temperature
Renal function	Need of renal replacement therapy, blood urea nitrogen concentrations, serum creatinine, creatinine clearance, serum urea, and occurrence of acute kidney injury
Liver function	Alanine aminotransferase/glutamic–pyruvic transaminase, aspartate aminotransferase/glutamic–oxaloacetic transaminase, alkaline phosphatase, bilirubin, albumin, arterial ketone body ratio
Coagulation and blood loss	Intra- and postoperative blood loss, postoperative haemoglobin, activated partial thromboplastin time, prothrombin time, and international normalised ratio
Metabolism	Blood glucose, insulin, ketone bodies, and free fatty acids
Electrolytes	Sodium, potassium, chloride, magnesium, and calcium
Other	Cost, markers of splanchnic dysoxia, and sequential organ failure assessment score

lactate-buffered solutions.[30–32,36–38,40,48] In the remaining four studies, divergent differences were reported between groups, with two studies favouring acetate-buffered solutions and two studies favouring lactate-buffered solutions.[20,21,24,25] The overall quality of evidence was low and downgraded because of risk of bias and imprecision (Supplementary material E).

Renal function was assessed in five studies,[20,25,29,38,41] amongst which a majority found no significant differences between groups.[20,25,29,38] Liver function was assessed by 10 studies,[26,27,30,35–39,41,48] with results indicating a possible association between administration of lactate-buffered solutions and a transiently decreased liver function.[27,36,37] The overall quality of evidence describing renal and liver function was very low and downgraded because of risk of bias, indirectness, and imprecision (Supplementary material E).

Coagulation status was assessed by six studies with no clear difference in outcome parameters between groups.[21,24,26,27,40,48] Measures of metabolism, assessed by nine studies, similarly showed no clear difference in effect depending on the type of buffered solution administered.[24,25,30,32,33,36,38,39,41]

Electrolyte status was addressed by 13 studies.[20,23–29,39–41,47,48] Sodium and potassium concentrations were largely unaffected by the use of differently buffered solutions.[24,25,27–29,40,41,48] Data regarding chloride[20,23–29,39] and calcium[20,40,47] concentrations were sparse and divergent. Plasma magnesium concentrations seemed to be higher in patients receiving acetate- *vs* lactate-buffered solutions; however, the data were sparse.[26,27,48] The overall quality of evidence assessing coagulation, metabolism, and electrolyte status was low and downgraded because of risk of bias and imprecision (Supplementary material E).

Discussion

In this scoping review, we found limited evidence on the use of the different types of buffered crystalloid solutions. The data were derived predominantly from surgical settings and indications for use were poorly described. The outcome measures lacked in general patient centredness, and the overall quality of evidence supporting the use of lactate- *vs* acetate-buffered solutions was low.

Most studies were performed in an elective surgical setting (i.e. intraoperative administration of buffered solutions); however, most studies did not specify the indication for use. Only five studies were performed outside the operating theatre, with the primary indication for use being fluid resuscitation.[20,22,28,34,35] Consequently, evidence is skewed regarding both population and indication for use. This highlights the need for further investigations on the use of lactate- *vs* acetate-buffered solutions outside the operating theatre, including in high-risk critically ill patients. It may be that this vulnerable population could be more susceptible to physiological changes caused by different buffered solutions; if so, this may cause heterogeneity in the treatment effect.[49]

The most commonly administered types of buffered crystalloid solutions were Ringer's lactate *vs* Plasma-Lyte or Ringer's acetate. Notably, the administration of buffered solutions was limited to short study periods with generally low volumes administered. It seems reasonable that a greater exposure to the intervention (i.e. increasing volumes or duration of fluid therapy) could potentially have a greater impact on patient-centred outcome measures. This supports the need for further trials investigating the use of lactate- *vs* acetate-buffered solutions in different settings.

We observed a considerable variation in the outcome measures described. The most commonly described outcomes were surrogate outcome measures targeting intermediate endpoints, such as improvement or correction of physiological or biochemical markers. This limits the clinical value of the results significantly, as non-patient-important outcomes (surrogate outcomes) are known to result in inflated estimates and increased risk of false-positive findings.[50,51]

Only seven studies reported patient-centred outcome measures,[20,21,23,26,34,45,46] none of which were high-quality RCTs. Importantly, no studies reported data on adverse effects. Failure to report information on adverse effects hampers the interpretation of the overall effects.[52,53]

Previous studies have assessed the effect of excess lactate and acetate *in vivo*, suggesting several possible undesirable effects associated with both buffering anions (Fig. 3).

Regarding acetate, animal studies have shown a significant increase in plasma concentrations of up to 40 times the physiological level with even small volumes of acetate-based

Table 2 Summary of results for each outcome category. BE, base excess; BUN, blood urea nitrogen; CI, confidence interval; LOS, length of stay; LVEF, left ventricular ejection fraction; OR, odds ratio; PL, Plasma-Lyte; POD, postoperative day; RA, Ringer's acetate; RL, Ringer's lactate; SF, Sterofundin; SOFA, sequential organ failure assessment; SPV, systolic pressure variation.

Outcome category	Specific outcome measures	Total no. of studies	Summary of results
Patient-centred outcome measures	Mortality (in-hospital, 28, 30, 60, and 90 days)	Six studies[20,21,23,26,34,46]	Five studies found no statistically significant difference between groups[20,21,23,26,34] One study found OR for 90-day mortality of 0.96 (95% CI: 0.94–0.97) in the acetate- *vs* lactate-buffered groups[46]
	Hospital LOS	Five studies[21,23,26,34,45]	Two studies found increased hospital LOS in the lactate- *vs* acetate-buffered groups[26,34] One study found increased hospital LOS in the acetate-buffered group[45] Two studies found no difference between groups[21,23]
	ICU LOS	Four studies[20,21,23,34]	No studies reported a significant difference in ICU LOS between groups[20,21,23,34]
	Postoperative and infectious complications	Four studies[21,26,34,46]	One study reported fewer days in ventilator in the acetate- *vs* lactate-buffered groups[34] One study found lower odds of respiratory failure in the acetate- *vs* lactate-buffered groups[46] One study found lower occurrence of cardiac arrythmias in the acetate- *vs* lactate-buffered groups[21] One study found that the total number of complications was lower in the acetate- *vs* lactate-buffered groups[26]
Acid/base status	Arterial blood gas describing levels of pH, BE, and hydrogen bicarbonate	Twenty-one studies[20–30,32–35,37–41,48]	Thirteen studies reported no significant difference in parameters between groups[20–22,25,26,29,30,32,34,35,38,40,48] Two studies found significantly lower pH in the acetate- *vs* lactate-buffered groups[23,33] Two studies found significantly lower pH in the lactate- *vs* acetate-buffered groups[24,28] Four studies found no difference in pH, but transiently higher BE in the acetate- *vs* lactate-buffered groups[27,37,39,41]
	Plasma lactate concentrations	Nineteen studies[20,21,23–27,29,30,32,34–41,48]	Fourteen studies reported increased plasma lactate concentrations in the lactate- *vs* acetate-buffered groups[21,23,24,26,27,29,30,34,36–39,41,48] Five studies found no significant difference in plasma lactate between groups[20,25,32,35,40]
	Plasma acetate concentrations	Seven studies[20,23,36–40]	Three studies found transiently increased concentrations of acetate in the acetate- *vs* lactate-buffered groups[23,38,39] Four studies found no significant difference between groups[20,36,37,40]
	Plasma gluconate/ pyruvate concentrations	Six studies[20,23,30,32,37,41]	Two studies found significantly higher gluconate in the acetate- *vs* lactate-buffered groups[20,23] One study reported significantly higher pyruvate in RA *vs* RL postoperatively[30] One study found transiently increased pyruvate in the lactate- *vs* acetate-buffered groups[37] Two studies found no significant difference in pyruvate concentrations between groups[32,41]
Haemodynamics		Twelve studies[20,21,24,25,30–32,36–38,40,48]	Eight studies found no significant difference in outcome parameters between groups at any time point[30–32,36–38,40,48] One study found that significantly more patients developed LVEF <50% in the RL *vs* PL group[20] One study reported an increased need of epinephrine in the RL *vs* RA group[21] One study reported significantly higher HR at 2–6 h in SF *vs* RL[24] One study found transiently increased HR, MAP, and SPV in the SF *vs* RL group[25]
Renal function		Five studies[20,25,29,38,41]	Four studies found no significant difference in renal function[20,25,29,38] One study found BUN significantly higher in RL *vs* RA at 2 and 6 h after fluid administration[41]
Liver function		Ten studies[26,27,30,35–39,41,48]	Seven studies found no significant difference in values depicting liver between groups at any time point[26,30,35,38,39,41,48] Three studies found transiently decreased liver function in the lactate- *vs* acetate-buffered groups[27,36,37]
Coagulation and blood loss		Six studies[21,24,26,27,40,48]	Two studies reported increased prothrombin time in the lactate- *vs* acetate-buffered groups[26,27] One study found increased blood loss intraoperatively in the lactate- *vs* acetate-buffered groups[26] One study found significantly lower haemoglobin concentrations postoperatively in the lactate- *vs* acetate-buffered groups[26]

Continued

Table 2 Continued

Outcome category	Specific outcome measures	Total no. of studies	Summary of results
			Four studies found no significant difference in measures between groups[21,24,40,48]
Metabolism		Nine studies[24,25,30,32,33,36,38,39,41]	Six studies reported no significant difference in blood glucose concentrations at any time point[25,30,32,33,36,38] Two studies found significantly higher glucose concentrations in the lactate- *vs* acetate-buffered groups, however, transiently[24,39] One study found significantly lower glucose concentrations in RL *vs* RA, however, only transiently[41]
Electrolytes	Sodium and potassium	Nine studies[24,25,27–29,39–41,48]	Eight studies reported no significant differences in sodium/potassium concentrations between groups[24,25,27–29,40,41,48] One study found transient but significantly increased sodium and potassium in the lactate- *vs* acetate-buffered groups[39]
	Chloride	Nine studies[20,23–29,39]	Six studies reported no significant difference in chloride concentrations between groups[20,24,25,27–29] Three studies found increased concentrations of chloride in the lactate- *vs* acetate-buffered groups[23,26,39]
	Magnesium	Three studies[26,27,48]	Three studies found increased concentrations of magnesium in the acetate- *vs* lactate-buffered groups[26,27,48]
	Calcium	Four studies[20,25,40,47]	Three studies found calcium significantly lower in the acetate- *vs* lactate-buffered groups at different time points[20,40,47] One study found significantly higher calcium in SF *vs* RL at 1 h and at end of surgery[25]
Other	Cost	Three studies[22,45,46]	One study found cost significantly higher in the acetate- *vs* lactate-buffered groups[22] Two studies found cost significantly lower in acetate- *vs* lactate-buffered groups[45,46]
	Measures of splanchnic dysoxia	One study[35]	One study found decreased gastric perfusion in the lactate- *vs* acetate-buffered groups[35]
	SOFA score	Two studies[20]	One study found significantly lower scores in the acetate- *vs* lactate-buffered groups on POD 3–6[34] One study reported no significant difference between groups[20]

crystalloid administered.[54–56] Furthermore, it has been suggested that acetate may decrease myocardial contractility and cause haemodynamic instability.[57–60] In the past, Ringer's acetate was routinely used in haemodialysis units, but, because of these findings, this practice has been discontinued.[58,61] Unlike acetate-buffered solutions, lactate-buffered crystalloids have the potential to increase plasma lactate and induce hyperglycaemia as lactate is a metabolically active compound used in gluconeogenesis.[11] Hence, excessive administration of lactated crystalloids may be a concern in the treatment of diabetic patients.[11,62] Moreover, as lactate is primarily metabolised in the liver, studies have questioned whether lactate-buffered solutions are appropriate for patients with reduced lactate metabolism attributable to acute or chronic liver failure.[11,63] Importantly, the aforementioned concerns are based on findings from experimental studies and theoretical conceptions; hence, the clinical impact is unknown.

It is possible that for many patients, the choice of buffered crystalloid solution does not significantly affect patient-centred outcome measures. However, as i.v. fluids are administered daily to many hospitalised adults, including those with critical illness, relatively small differences in benefit, harm, or cost per patient will result in sizeable overall effects.

For many years, i.v. fluid therapy has been guided by physiological principles rather than results of clinical trials.[64] Results from RCTs have shown that i.v. fluid therapy can negatively affect patient-centred outcomes depending on the type of fluid. Administration of colloids, such as albumin, increases mortality in patients with traumatic brain injury,[65] whilst patients with sepsis receiving hydroxyethyl solutions are at increased risk of acute kidney injury and maybe death.[66]

Based on the results of recent RCTs[12–15] and several reviews,[8,9,11,67–69] clinical practice guidelines recommend buffered crystalloid solutions as first choice for i.v. fluid treatment.[70] Although buffered crystalloid solutions have physiological appeal given their part resemblance to plasma water,[11,71] strong evidence is still lacking for the use of the specific buffered solutions. The choice of fluid administered should be based on the scientific evidence available and not on intrinsic biases, favouring a specific theoretical pharmaceutical profile.[72,73]

This scoping review identified several ongoing trials comparing the use of lactate- *vs* acetate-buffered solutions,[42–44] indicating that the topic is receiving attention, acknowledging the pending need for evidence on the use of lactate- *vs* acetate-buffered solutions. Specifically, the results of the large BASE trial[44] (expected n=2093), investigating the effect of differently buffered solutions on several patient-important outcome measures in critically ill patients, are awaited with great interest.

This scoping review demonstrates the need for further evidence on the use of acetate- *vs* lactate-buffered solutions, including indications for use. Large-scale clinical trials are needed both to assess the potential benefits and harms of i.v.

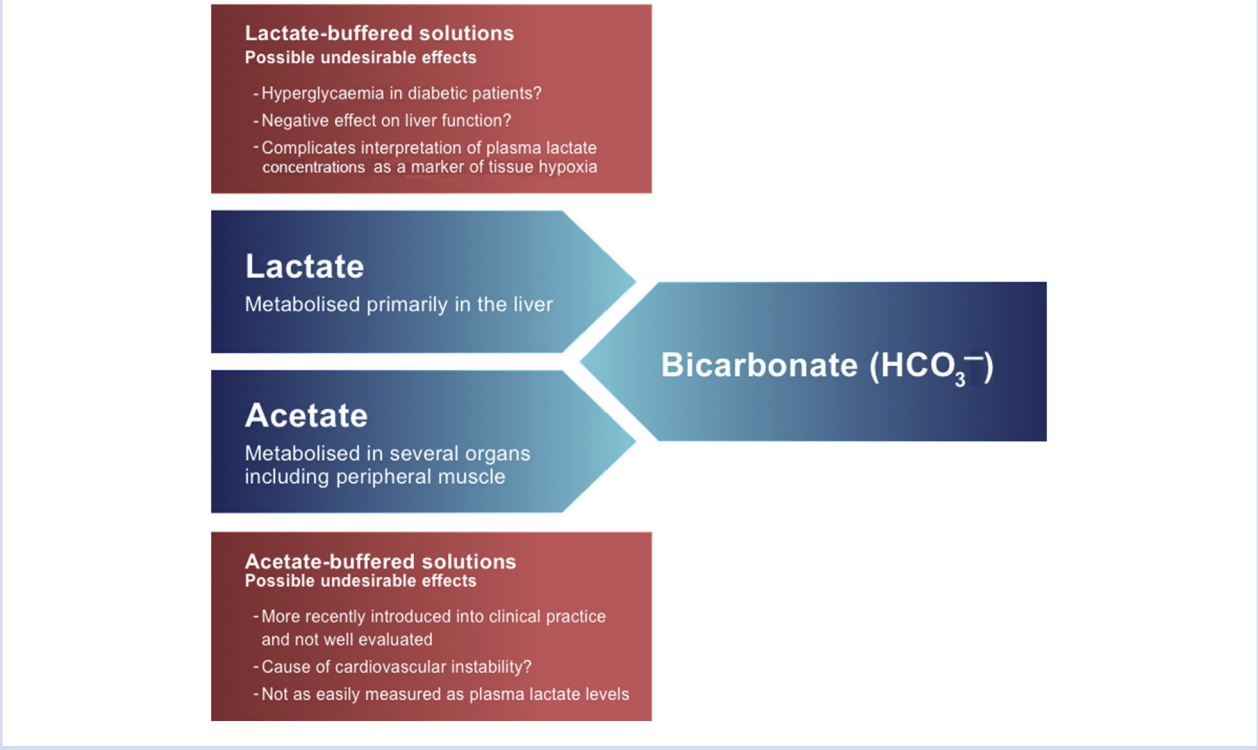

Fig 3. Potential undesirable effects of alternative buffers.

fluid treatment with lactate- *vs* acetate-buffered crystalloids, and to determine the appropriate indications for their individual use.

It is evident from the results of this review that existing fluid trials have inherent methodological limitations, especially regarding clinical heterogeneity. It is therefore important to make sure that the trial population represents the general population of interest and that timing, indication, duration, and dosing are specified. Similarly, physiological targets should be pre-specified and outcomes should be important to patients. Ideally, the methodology should be aligned across studies to allow for meaningful comparison through meta-analyses (i.e. by development of a core outcome set for fluid trials).[74]

Strengths and limitations

The strengths of our scoping review include a comprehensive and systematic literature search with no language restriction, a pre-published protocol,[18] adherence to the PRISMA-ScR statement,[17] and assessment of the quality of evidence according to GRADE.[19]

Our review also has limitations. First, we cannot be sure that our search string identified all relevant studies. Second, trials in languages other than English/Scandinavian were translated using Google Translate, which may have led to misinterpretations. Importantly, there were no disagreements between the authors during screening or data extraction. Third, we chose to exclude studies in children and healthy subjects, limiting the scope of the population. Fourth, we did not assess risk of bias in detail, which may reduce the transparency of results and findings somewhat. Finally, variation in the population and intervention of interest give rise to some degree of heterogeneity.

Conclusions

This scoping review demonstrates that the quantity and quality of evidence on the use of different buffered crystalloid solutions are low, derive primarily from surgical settings, and rarely report patient-important outcome measures, and the balance between the benefits and harms is largely unknown.

Authors' contributions

Study design: KLE, AP, MHM
Data collection: KLE, MMJ
Data analysis: KLE
Drafting of paper: KLE
Revision of paper for critically important intellectual content: AP, MMJ, MHM
All authors approved the final version of the paper.

Declarations of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.07.017.

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