Isotonic crystalloid solutions: a structured review of the literature

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Editor's key points

- There is renewed interest in perioperative fluid therapy.
- The authors have systematically reviewed literature related to crystalloid solutions.
- Despite similar haemodynamic profiles, different crystalloid solutions have varying effects on electrolyte balance and end-organ function.

Background. Several different crystalloid solutions are available for i.v. fluid administration but there is little information about their specific advantages and disadvantages.

Methods. We performed a systematic search of MEDLINE, EMBASE, and CENTRAL up until May 17, 2012, selecting all prospective human studies that directly compared any near-isotonic crystalloids and reported any outcome.

Results. From the 5060 articles retrieved in the search, only 28 met the selection criteria. There was considerable heterogeneity among the studies. Several articles reported an increased incidence of hyperchloraemic acidosis with the use of normal saline, and others an increase in blood lactate levels when large amounts of Ringer’s lactate solutions were infused. From the limited data available, normal saline administration appears to be associated with increased blood loss and greater red blood cell transfusion volumes in high-risk populations compared to Ringer’s lactate. Possible effects of the different solutions on renal function, inflammatory response, temperature, hepatic function, glucose metabolism, and splanchnic perfusion are also reported. The haemodynamic profiles of all the solutions were similar.

Conclusions. Different solutions have different effects on acid–base status, electrolyte levels, coagulation, renal, and hepatic function. Whether these differences have clinical consequences remains unclear.

Keywords: crystalloid solutions; infusions, intravenous; isotonic solutions

Crystalloids are the most widely used i.v. solutions and are administered at some time to almost all acutely ill patients. A primary goal of i.v. fluid therapy is to restore and maintain sufficient blood volume to guarantee adequate transport of oxygen and nutrients to the tissues. Each type of i.v. fluid has certain advantages compared with other fluids but also some shortcomings. Recent studies have focused on the safety of various colloid solutions, but less attention has been paid to the effects of different isotonic crystalloid solutions.

The most widely used i.v. crystalloid solutions differ considerably from human plasma in composition, tonicity, or both. The most frequently prescribed crystalloid solutions are normal saline and Ringer’s lactate solutions. Possible negative effects of these solutions on acid–base status and plasma tonicity prompted the development of so-called ‘balanced’ solutions, the most widely used being PlasmaLyte (Baxter, Deerfield, IL, USA) in which some of the negative ions (chloride and lactate) are replaced with acetate and gluconate. Nevertheless, none of these solutions is completely physiological and all may have unwanted effects.

Because of the potential clinical differences between solutions and the lack of definitive data, we conducted a systematic review of all prospective, randomized, controlled trials that have compared different crystalloid solutions in order to assess the available evidence.

Methods

We conducted a search of the literature using MEDLINE, EMBASE, and CENTRAL databases, on May 17, 2012, looking for all articles that had prospectively compared different near-isotonic crystalloid solutions. The details of the search strategy are presented in the Supplementary material. The inclusion criteria were: (i) human studies in the adult population; (ii) prospective randomized clinical trials (RCT) of two or more pure cohorts of near-isotonic i.v. solutions; (iii) results reported for any outcome parameters; and (iv) at least 20 subjects included. In studies with additional cohorts comparing colloids, hypertonic, or hypertoncotic solutions, we attempted to extract the data for the pure near-isotonic crystalloid cohorts. We excluded from our analysis studies of hypertonic solutions or hyperosmolar solutions, studies in children, studies using topical or other routes of application, studies comparing specific ingredients, such as magnesium or bicarbonate, and studies
of parenteral nutrition. Study selection was performed without limits of date of publication or language. If the article was not in English, it was translated by a native speaking colleague. We completed the search by reviewing the bibliographies of every selected article to look for possible additional articles that had not been retrieved by the search.

Two authors (D.O.C. and A.R.B.) independently selected the articles based on the criteria above; any discrepancy was resolved by consensus. The reference data, populations, and outcomes were then extracted from the articles into pre-specified tables. The quality of all studies was evaluated using the Jadad scale.

There was considerable heterogeneity in the design of the studies in terms of the type and amount of fluid given, study population, fluid indication (maintenance and resuscitation), duration of fluid administration, and outcome studied, making it impossible to conduct a formal meta-analysis of all the outcomes. However, for some outcomes (pH and lactate levels, red blood cell transfusion, blood loss, creatinine levels, and urine output) obtained from studies comparing normal saline with Ringer’s lactate, a meta-analysis was performed because they were reported systematically in these populations. The estimated mean effect of each study of these outcomes was calculated with the respective 95% confidence intervals and the global effect was then assessed using a Der-Simonian–Laird random effects model.8 Results are presented as Forest plots with estimates of heterogeneity. All analyses were performed using MetaEasy 1.0.4 (Statanalysis, UK).

Results

We identified a total of 5060 articles but only 28 studies met the selection criteria and were retained for the descriptive analysis (Fig. 1). Seven of the articles were not in English and were translated before extracting the data. The included studies are given in Table 1.

Types of fluids compared

Some studies had three treatment cohorts so they were included in more than one group. The differences between normal saline and Ringer’s lactate were explored in 21 studies, between PlasmaLyte and another near-isotonic solution in 7 studies, and between Ringer’s acetate and another near-isotonic solution in 3 studies. A complete description of the study comparisons is given in Table 2. The administered doses and duration of exposure were extremely variable (Table 1); doses ranged from 500 to 7000 ml and the duration between 20 min and 48 h.

Studied populations

Only six studies were performed in non-surgical populations with cohorts of between 10 and 32 patients. The other 22 studies were performed in diverse surgical patients undergoing scheduled procedures with cohorts of between 10 and 54 patients. The most commonly studied population was renal-transplant patients who were included in five studies.

Effects on outcome measures

Haemodynamics

All studies showed similar haemodynamic effects with each of the crystalloid solutions studied. Ten studies reported no significant differences between crystalloids in amount of volume required, the need for vasoactive drugs, or the time to achieve resuscitation. In a study by Kashimoto and colleagues comparing Ringer’s lactate with Ringer’s acetate, there was a trend towards a higher fingertip blood flow with Ringer’s acetate, which may reflect the vasodilating properties of acetate, but interpretation is limited by the small population studied.

Acid–base state and electrolyte concentration

Twenty-two of the 23 articles that explored the effects on acid–base status showed that the administration of normal saline was associated with a decrease in blood pH, an increase in chloride levels, and a decrease in bicarbonate or strong ion difference (SID); the study by Deng and colleagues reported a similar trend, but without statistical significance. Most of the fluids were administered over a short period and these changes resolved in the subsequent hours. The largest difference in pH levels was reported in the study by Scheingraber and colleagues, who noted a pH of 7.28 with normal saline compared with 7.40 with Ringer’s lactate after infusing 60 ml kg⁻¹ of fluid over 2 h.

Takil and colleagues randomized 30 patients undergoing elective spinal surgical procedures to preoperative Ringer’s lactate or normal saline. These authors reported two main findings: transient intraoperative hyperchloraemic acidosis in
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<th>Study</th>
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<tr>
<td>Ramanathan and colleagues</td>
<td>Elective Caesarean</td>
<td>NS (15) RL (15) PL (15)</td>
<td>BA: 1200 ml in 1 h</td>
<td>NS decrease in pH</td>
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<td>Veroli and Benhamou</td>
<td>Minor orthopaedic surgery with lumbar epidural anaesthesia</td>
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<td>McFarlane and Lee</td>
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<td>NS (15) PL (15)</td>
<td>Intraoperative: 15 ml kg^{-1} h^{-1}</td>
<td>Greater increase in postoperative chloride using NS</td>
<td>Greater decrease in BE and HCO_{3} with NS concordant with hyperchloraemic acidosis.</td>
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<td>Butscher and colleagues</td>
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<td>NS (10) RL (10)</td>
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<td>Greater decrease in osmolarity after RL</td>
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<td>Kashimoto and colleagues</td>
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<td>RA (15) RL (15)</td>
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<td>Scheingraber and colleagues</td>
<td>Lower gynaecological system procedures</td>
<td>NS (12) RL (12)</td>
<td>Intraoperative: 30 ml kg^{-1} h^{-1}</td>
<td>Lower pH at second hour with NS</td>
<td>Lower values of BE, lactate, and calculated SID at 2 h with NS.</td>
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<td>Deng</td>
<td>Hysterectomy and myomectomy</td>
<td>NS (12) RA (12)</td>
<td>Intraoperative: 20 ml kg^{-1} h^{-1}</td>
<td>Lower pH at 120 min with NS</td>
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<td>waters and colleagues</td>
<td>Aortic reconstructive surgery</td>
<td>NS (33) RL (33)</td>
<td>Intraoperative: titrated during surgery. The mean volume of 6871 ml with RL and 7000 ml with NS</td>
<td>Greater decrease in intraoperative pH with NS</td>
<td>Greater decrease in intraoperative HCO_{3} and BE, higher levels of Cl^{-}, greater need for blood product transfusions and greater urine output with NS. No significant changes in lactate levels, ventilation hours or LOS.</td>
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<td>Takil and colleagues</td>
<td>Elective major spine surgery</td>
<td>NS (15) RL (15)</td>
<td>Intraoperative and 12 h postoperative: 20 ml kg^{-1} h^{-1} intraoperative and 2.5 ml kg^{-1} h^{-1} thereafter</td>
<td>Transient respiratory acidosis in first postoperative hours with RL</td>
<td>Transient hyperchloraemic acidosis (pH, HCO_{3}^{-}, and BE) intraoperative and until 12 h postoperative with NS. Mild hyponaatraemia in first postoperative hours with RL. No significant differences in crystalloid volume, urinary output, and blood losses.</td>
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<td>O’Malley and colleagues</td>
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<td>NS (26) RL (25)</td>
<td>Intraoperative: titrated during surgery. Mean volume of 5600 ml with RL and 6100 ml with NS</td>
<td>No differences in creatinine at postoperative third day, 1 week or 6 months</td>
<td>More cases of hyperkalaemia, use of intraoperative HCO_{3} and higher Cl^{-} levels at end of surgery with NS. No significant differences in blood loss or patients transfused.</td>
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<td>Chin and colleagues&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Elective surgery in non-diabetic patients</td>
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<td>Karaca and colleagues&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Transurethral prostatic procedures under spinal anaesthesia</td>
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<td>Elective Coesarean</td>
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<td>Intraoperative: bolus of 2000 ml and 2 ml kg&lt;sup&gt;-1&lt;/sup&gt; h&lt;sup&gt;-1&lt;/sup&gt; thereafter</td>
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<td>Rhabdomyolysis induced by doxylamine intoxication</td>
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<td>Telman and colleagues&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Sigmoid diverticulosis undergoing left hemicolectomy</td>
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<td>Higher lactate levels with RL at the end of surgery</td>
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<td>Anki and colleagues&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Burns &gt;30% of TBSA</td>
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<td>Nuraei and colleagues&lt;sup&gt;15&lt;/sup&gt;</td>
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<td>NS (54)  RL (54)</td>
<td>Intraoperative: protocol to maintain CVP. Mean volume of 3125 ml with RL and 3005 ml with NS</td>
<td>No differences in pH at the end of surgery</td>
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<td>Right hepatectomy for liver transplantation</td>
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<td>Intraoperative: titrated during surgery. Mean volume of 3407 ml with RL and 3302 ml with PL</td>
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<td>Mahler and colleagues&lt;sup&gt;11&lt;/sup&gt;</td>
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<td>Wu and colleagues&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Acute pancreatitis</td>
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<td>Rehydration protocol (24 h). Boluses of 20 ml kg&lt;sup&gt;-1&lt;/sup&gt; and infusion of 3 ml kg&lt;sup&gt;-1&lt;/sup&gt; h&lt;sup&gt;-1&lt;/sup&gt;</td>
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<td>Heidari and colleagues&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Lower abdominal surgery</td>
<td>NS (30)  RL (30)</td>
<td>BA: 15 ml kg&lt;sup&gt;-1&lt;/sup&gt; h&lt;sup&gt;-1&lt;/sup&gt; bolus</td>
<td>Less vomiting at 6 h with RL</td>
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<sup>Continued</sup>
the normal saline group and an early postoperative increase in $P_{a}CO_2$ and bicarbonate levels in the Ringer’s lactate group; the latter finding was interpreted to be the result of lactate metabolism to CO$_2$. Cho and colleagues$^{26}$ showed that the hyperchloraemic acidosis was accompanied by a concomitant decrease in urinary pH in patients treated with normal saline for rhabdomyolysis. These changes can be explained by the need for the kidney to eliminate the chloride load.

In a meta-analysis of the studies comparing normal saline with Ringer’s lactate that reported this outcome before and after fluid administration, use of normal saline was correlated with the development of hyperchloraemic acidosis (Fig. 2) and this effect was similar when considering only studies of surgical populations or patients undergoing kidney transplantation (Supplementary material, Figs S1 and S2).

Blood lactate concentrations

Five studies$^{14,16,20,28,30}$ showed an increase in lactate levels with Ringer’s lactate compared with other solutions. Two studies$^{21,29}$ showed a trend in the same direction but without statistical significance and one study$^{12}$ showed no change in lactate levels when comparing Ringer’s lactate with normal saline in a population of hepatic transplant patients. McFarlane and Lee$^{18}$ compared the lactate-free solutions, PlasmaLyte and normal saline, in patients undergoing scheduled major hepatobiliary or pancreatic surgery and reported no significant differences in blood lactate levels. Deng and colleagues$^{10}$ reported higher lactate levels comparing Ringer’s acetate with normal saline when used in women undergoing scheduled hysterectomy. The largest difference in lactate levels was reported in a study by Scheingraber and colleagues$^{20}$ who noted, after infusing 60 ml kg$^{-1}$ of fluid over 2 h, a serum lactate of 0.4 mmol litre$^{-1}$ for patients given normal saline compared with 2 mmol litre$^{-1}$ for Ringer’s lactate. In a meta-analysis of data from the studies comparing normal saline with Ringer’s lactate that reported this outcome, the same association (i.e. greater lactate levels with Ringer’s lactate solutions) was found (Fig. 3).

Coagulation and bleeding

Ten studies$^{12,13,18,20–23,27,29,30}$ investigated the effects on bleeding, need for transfusion of blood products, or other aspects of coagulation. In patients undergoing major
scheduled hepatobiliary or pancreatic surgery, McFarlane and Lee\textsuperscript{18} reported an identical bleeding risk with PlasmaLyte and normal saline. Seven studies comparing normal saline with Ringer’s lactate\textsuperscript{12 13 20–23 27} found no significant differences between the fluids in blood loss or need for transfusion; Waters and colleagues\textsuperscript{21} reported, in a high-risk population of patients undergoing aortic reconstructive procedures, an increased need for blood product transfusions in those who received normal saline. In a meta-analysis of the data from the studies comparing normal saline with Ringer’s lactate that reported this outcome in millilitres, there were no differences regarding the volume of blood lost. We also performed a subgroup analysis of these studies, dividing them according to the volumes of blood loss reported in each study into those that included high-risk and those with low-risk patients, using a cut-off point of 800 ml, which is roughly 15% of the average blood volume (the limit of a Grade II hemorrhage). In this subgroup analysis, there was increased blood loss with
normal saline (Fig. 4) in the high-risk patients. No differences were found when grouping studies according to renal transplant or non-renal transplant populations (Supplementary material, Figs S3 and S4). When considering data regarding the volume of transfused red blood cells reported in millilitres, greater transfusion volumes were reported in patients receiving normal saline (Fig. 5).

Just two studies reported effects on measures of coagulation: Shin and colleagues\(^30\) noted an increase in the International Normalized Ratio (INR) after infusion of Ringer's lactate compared with PlasmaLyte, and Aoki and colleagues\(^29\) found no differences in antithrombin (AT) III levels after infusion of Ringer's acetate or Ringer's lactate.

**Renal function**

Eleven studies\(^{15\ 20–24\ 26–28\ 32\ 35}\) explored renal function after exposure to different crystalloids. Five studies in high-risk post-renal-transplant patients reported no significant differences between normal saline, Ringer's lactate, and PlasmaLyte.\(^{15\ 23\ 27\ 28\ 33}\) When evaluating only comparisons of normal saline and Ringer's lactate, seven studies\(^{15\ 20–23\ 27\ 28}\) reported data on diuresis and two\(^{21\ 28}\) showed significant opposite differences in urine output. For meta-analysis purposes, we took the first urine output measure expressed in millilitres or the first creatinine level reported after the first 24 h of fluid administration. There were no differences between solutions for any outcome (Fig. 6). Results of meta-analyses of the data showed no differences between solutions in renal-transplant or non-renal transplant patients (Supplementary material, Figs S5–S7). Meta-analysis of studies reporting creatinine levels 3 days after renal transplantation showed no differences between the two solutions (Supplementary material, Fig. S8).

**Inflammation**

Wu and colleagues\(^{32}\) reported a more rapid decrease in the prevalence of the systemic inflammatory response syndrome after the first 24 h and a greater decrease in blood C-reactive protein (CRP) levels with Ringer’s lactate than with normal saline in patients with acute pancreatitis. No other studies were found on this topic.

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**Fig 3** Forest plot of lactate levels before (A) and after (a) fluid administration in studies comparing normal saline with Ringer’s lactate.
Fig 4. Forest plot of blood loss volumes in studies comparing normal saline with Ringer’s lactate when considering all patients (a), patients with a low risk of bleeding (b), and patients with a high risk of bleeding (c).
Glucose concentration

Four studies\(^9\, 14\, 16\, 24\) found no difference in blood sugar levels after infusion of any study solution in non-diabetic populations. Two studies compared different crystalloids in patients with ketoacidosis: Mahler and colleagues\(^31\) reported a greater degree of hyperchloraemic acidosis with normal saline than with PlasmaLyte; and Van Zyl and colleagues\(^36\) observed that the time to reach normalization of glycaemia was shorter with normal saline than with Ringer’s lactate.

Liver metabolism

In donors undergoing right hepatectomy, Shin and colleagues\(^30\) reported that, compared with PlasmaLyte, Ringer’s lactate may have been associated with hepatic dysfunction, as measured by a transient increase in bilirubin and mild prolongation of prothrombin time during the first 2 days and a decrease in albumin levels during the first 4 days. These transient changes were, however, not clinically relevant; there were no differences in liver enzymes, and no increased need for transfusion.

Splanchnic dysoxia

Aoki and colleagues\(^29\) used gastric tonometry to evaluate the degree of splanchnic dysoxia during the resuscitation of adult burns patients. The gastric \(P_{CO_2}\) gap was reduced in the first 72 h in patients resuscitated with Ringer’s acetate compared with those resuscitated with Ringer’s lactate. There were no differences in the amounts of fluid administered, urinary output, or mean arterial pressure. The study was limited by the small sample size (20 patients) and a randomization process by alternate allocation.

Temperature

Kashimoto and colleagues\(^19\) reported a smaller decrease in central body temperature with Ringer’s acetate than with Ringer’s lactate during isoflurane anaesthesia. The physiological explanation for this result is unclear, but could be related to acetate-induced vasodilatation or peripheral metabolism and heat production under acetate perfusion.

Nausea and vomiting

Two studies explored the development of nausea and vomiting after anaesthesia. Heidari and colleagues\(^33\) reported less vomiting in the first 6 postoperative hours with Ringer’s lactate compared with normal saline, but Karaca and colleagues\(^11\) reported no differences.

Discussion

I.V. fluid administration is one of the most widely used interventions in hospitalized patients and yet our literature review underlines the paucity of good trials on this important topic. The studies were small and generally of low quality (15 of the 28 studies had a Jadad score of < 3). The studies were also very heterogeneous in terms of patient populations, amounts and duration of fluid given, timing of fluid in relation to surgery when performed, the type of crystalloid used, and the outcome reported. It was, therefore, not possible to make any global statement related to effects on mortality or morbidity, including length of stay, need for organ support, haemostasis, or gastrointestinal complications.

There is a clear association between normal saline infusion and the development of hyperchloraemic acidosis. Studies in healthy volunteers have shown the same association.\(^37\, 39\) This metabolic effect is expected, because the administration...
of chloride ions diminishes the anion gap and bicarbonate is used as a buffer to compensate; alternatively, the increase in chloride levels decreases the SID, which affects the dissociation of water into hydrogen ions. Several studies defined hyperchloraemic acidosis as a principal outcome measure, but none tried to correlate its appearance with other clinically important outcomes such as length of stay, renal function, inflammation, or mortality. In a retrospective study, Gunnerson and colleagues tried to quantify the impact of different types of acidosis on the outcomes of intensive care unit (ICU) patients. These authors collected data from a period of 18 months and a total of 851 patients were analysed. There was a clear association of lactic acidosis but not of hyperchloraemic acidosis with mortality.

In vitro dilutional studies using different thromboelastography (TEG) techniques have shown that the use of normal saline may be associated with a hypocoagulable state and Ringer’s lactate with a hypercoagulable state, as expressed by the clotting time, the amplitude of coagulation, or thrombin generation. In an uncontrolled haemorrhagic pig model, Kiraly and colleagues reported an increase in blood losses, prolongation of coagulation times and more TEG alterations with the use of normal saline compared with Ringer’s lactate. Whether these in vitro and animal studies can be translated into clinical practice is unclear, but our data do tend to support a greater risk of bleeding with normal saline, perhaps particularly in populations at high risk of bleeding; nevertheless, our results must be interpreted with caution because of the methodological limitations already discussed. More prospective studies are needed on this topic.

Hyperchloraemic acidosis may also result in renal vasoconstriction. In a denervated and autotransplanted kidney model,

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**Figure 6** Forest plot of first reported urinary output volume (A) or creatinine level (B) after the first 24 h of fluid administration in studies comparing normal saline with Ringer’s lactate.
in dogs, Wilcox showed transient renal vasoconstriction related to the chloride content of different hypertonic solutions. The administration of chloride results in free water retention. Interestingly, a delayed initiation of diuresis was observed in studies that compared normal saline with Ringer’s lactate in healthy volunteers. However, in the studies included in our review, there were no major differences in renal function between solutions in different populations, even after renal transplantation. Nevertheless, whether renal function may deteriorate secondary to hyperchloraemic acidosis induced by normal saline administration deserves further study.

Romanelli and colleagues injected Ringer’s lactate or normal saline for 5 s into the coronary arteries of patients undergoing coronary angiograms and showed more electrocardiogram alterations in the normal saline than in the Ringer’s lactate group. Unal and colleagues used the same solutions topically after nasal sepsal surgery and demonstrated that normal saline impaired mucociliary function more than Ringer’s lactate. Clearly, more research is needed to define the effects of hyperchloraemic acidosis induced by normal saline on metabolism, inflammation, renal function, coagulation, and even mortality.

The replacement of some of the chloride by lactate in Ringer’s lactate solution was proposed by Dr Hartmann, a paediatrician, so that it is not surprising that the solution is hypotonic. Blood lactate levels increase with administration of large amounts of Ringer’s lactate, and Jackson and colleagues noted the possible spurious hyperlactataemia when blood is drawn from the line where the solution is infused. However, Didwania and colleagues reported no differences in the measured levels of lactate in healthy adult volunteers receiving normal Ringer’s lactate infusion rates. There is a clear association of lactate levels with mortality, but no evidence that lactate induces damage. In contrast, lactate may be used as a fuel for the myocardium, the neurones, red blood cells, and other cells. Normal lactate in the body appears as the 1-isomer and humans are probably unable to metabolize the D-isomer easily. In the studies in our review, the exact composition of the Ringer’s lactate used was not defined although many commercially available solutions use a racemic mixture of both isomers. Some studies have compared the two isomers in infused solutions and reported potential alterations in the lung and inflammatory system with the D-isomer, but these findings are not conclusive.

We know relatively little about the effects of the acetate and gluconate that replace some of the chloride content in some fluids. Ringer’s acetate solutions may create metabolic alterations. Inoue and colleagues explored acetate metabolism using a liver rat model and showed that Ringer’s acetate was associated with pyrophosphate accumulation inside the mitochondria, a phenomenon that could potentially lead to mitochondrial dysfunction. In the past, Ringer’s acetate was used routinely in haemodialysis units, but these limitations and studies suggesting a vasodilatory and cardio-depressant effect of acetate have restricted its use. The haemodynamic effects of PlasmaLyte have been less well studied than those of the other crystalloid solutions, and further studies are needed to evaluate the possible deleterious effect of the acetate when PlasmaLyte is used in large amounts or for prolonged periods of time. PlasmaLyte also includes gluconate, which is probably the reason for false-positive galactomannan tests, a biomarker used for early diagnosis of invasive pulmonary aspergillosis, in patients who have received Plasma-Lyte. This effect may not be detrimental, but we actually know very little about the metabolism and safety of gluconate. Some early studies explored the oral administration of gluconic acid and showed that its metabolites were excreted in the urine and associated with urinary acidification in humans. Gluconate appears spontaneously in nature and seems to be very well tolerated by living organisms. Bacteria have a specialized metabolic cycle known as the Entner–Doudoroff pathway, which enables them to use gluconate as a source of fuel, but although it is a molecule similar to glucose, there is no clear evidence that human beings can incorporate it as a fuel source. If we cannot introduce it into the glycolysis pathway, then hepatic metabolism or urinary excretion is expected. However, these aspects need to be clarified.

Although PlasmaLyte may offer some advantages over Ringer’s lactate or normal saline in terms of acid–base status, there are concerns about its safety profile. Some data from the industry have suggested different energetic costs with the different solutions, as expected by their different metabolism, but other studies suggested no differences, such as that by Zadak and colleagues, who directly measured oxygen consumption (VO2) by indirect calorimetry in healthy subjects and found no significant differences between PlasmaLyte and Ringer’s acetate. More relevant are data from a pig model of severe haemorrhagic shock showing that PlasmaLyte was associated with a higher fatality rate compared with normal saline or Ringer’s lactate. These investigators suggested that the acetate or magnesium contents of PlasmaLyte were a possible explanation for these findings. Our review was limited to prospective RCTs. However, it is worth mentioning two recent non-randomized studies. Using a propensity analysis, Shaw and colleagues suggested, in a retrospective evaluation of patients undergoing open major abdominal surgery, that patients who received normal saline had increased development of infections and renal failure requiring dialysis, increased blood transfusion requirements, increased electrolyte disturbances, and increased acidosis treatment compared with those who received PlasmaLyte. Yunus and colleagues compared two periods, one in which chloride-liberal solutions were given and the other in which chloride-restrictive solutions were used, and reported that the chloride-restrictive period was associated with a decrease in the development of acute renal failure. If we assume that the differences reside only in the administered crystalloid, a good explanation for these differences could be related to the development of hyperchloraemic acidosis. The main limitation of these non-randomized studies lies in the fact that we cannot exclude the possibility that those who received PlasmaLyte were less ill, with a lower risk of complications.

This extensive review included all publications without language restrictions, making it the most complete on this topic.
However, we still know very little about the effects of the crystalloids that we infuse into so many patients. Do we, therefore, need a large RCT comparing the effects of crystalloids on morbidity and mortality? We are not convinced, for two reasons: first this would require a large number of patients to detect any potential difference; secondly and more importantly, crystalloids may not be ‘one size fits all’ fluids and should be considered more as drugs that need to be individually prescribed based on the patient’s inflammatory, acid–base, renal, and coagulation profiles. There is currently no completely physiological solution without side-effects that we can administer safely and indiscriminately to all patients. It may be more appropriate to study specific questions, such as the effects on renal function or haemostasis, in well-defined groups of patients.

Conclusions
Each near-isotonic crystalloid solution has a different profile in terms of impact on acid–base status, electrolyte levels, coagulation, inflammation, renal, and hepatic function. Whether these differences lead to deleterious effects or affect prognosis remains unresolved. The choice of the best near-isotonic solution for each patient resides in a complete understanding of the expected response to each solution and the patient’s risk factors.

Supplementary material
Supplementary material is available at British Journal of Anaesthesia online.

Authors’ contributions
D.O.C.: study design, literature search and synthesis, and first draft of manuscript. A.R.B.: literature search and synthesis, and first draft of manuscript. J.L.V.: study design and critical review of manuscript.

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References
12 Deng LH. Influence of transfusion of lactated Ringer’s solution on arterial blood lactate concentration and acid base balance during orthotopic liver transplantation. Chin J Mod Nurs 2008; 14: 1457
24 Chin KJ, Macachor J, Ong KC, Ong BC. A comparison of 5% dextrose in 0.9% normal saline versus non-dextrose-containing crystalloids as the initial intravenous replacement fluid in elective surgery. Anaes Intensive Care 2006; 34: 613 – 7
45 Kellum JA, Song M, Almasi E. Hyperchloremic acidosis increases circulating inflammatory molecules in experimental sepsis. Chest 2006; 130: 962 – 7
47 Brummel-Ziedins K, Whelihan MF, Ziedins EG, Mann KG. The resuscitative fluid you choose may potentiate bleeding. J Trauma 2006; 61: 1350 – 8
48 Kiraly LN, Differding JA, Enomoto TM, et al. Resuscitation with normal saline (NS) vs. lactated ringers (LR) modulates hypercoagulability and leads to increased blood loss in an uncontrolled hemorrhagic shock swine model. J Trauma 2006; 61: 57 – 64


68 Mochizuki M. 4-Week oral toxicity study of sodium gluconate (FR2531). Final report No. BOZO/B-2966. Tokyo: Gotemba Laboratory, Bozo Research Center, 1995


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