Original Article

Balanced versus isotonic saline resuscitation—a systematic review and meta-analysis of randomized controlled trials in operation rooms and intensive care units

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Contributions: (I) Conception and design: A Serpa Neto, RB Klanderman, I Martin Loeches, P Pelosi, MJ Schultz; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: A Serpa Neto, RB Klanderman, I Martin Loeches, P Pelosi, MJ Schultz; (V) Data analysis and interpretation: A Serpa Neto; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Fluid resuscitation is the cornerstone in treatment of shock, and intravenous fluid administration is the most frequent intervention in operation rooms and intensive care units (ICUs). The composition of fluids used for fluid resuscitation gained interest over the past decade, with recent focus on whether balanced solutions should be preferred over isotonic saline.

Methods: Systematic review and meta-analysis of randomized controlled trials (RCTs) comparing fluid resuscitation with a balanced solution versus isotonic saline in adult patients in operation room or ICUs. Primary outcome was in-hospital mortality, secondary outcomes included occurrence of acute kidney injury (AKI) and need for renal replacement therapy (RRT).

Results: The search identified 11 RCTs involving 2,703 patients; 8 trials were conducted in operation room and 3 in ICU. In-hospital mortality, as well as the occurrence of AKI and need for RRT was not different between resuscitation with balanced solutions versus isotonic saline, neither in operation room nor in ICU patients. Serum chloride levels, but not arterial pH, were significantly lower in patients resuscitated with balanced solutions.

Conclusions: Currently evidence insufficiently supports the use of balanced over isotonic saline for fluid resuscitation to improve outcome of operation room and ICU patients.

Keywords: Balanced solution; isotonic saline; fluid resuscitation; operation room; intensive care unit (ICU); systematic review; meta-analysis; normal saline; chloride

Submitted Jul 04, 2017. Accepted for publication Jul 21, 2017.
doi: 10.21037/atm.2017.07.38
View this article at: http://dx.doi.org/10.21037/atm.2017.07.38

Introduction

Stabilization of hemodynamics is a key intervention in patients with shock, and usually requires intravenous infusion of fluids (1). Worldwide isotonic saline is the most commonly used solution for fluid resuscitation (2). Dilutional or hyperchloremic metabolic acidosis is a well-known side-effect of infusion of large amounts of isotonic saline, which could be prevented with the use of balanced crystalloid solutions (3,4).

Balanced crystalloid solutions more closely resemble the electrolyte composition of plasma (5). The potential clinical benefit from resuscitation with balanced solutions comes from the lower chloride content, as development of dilutional acidosis could increase the inflammatory response (6,7), and decrease splanchnic perfusion (8), myocardial contractility (9) and the cardiovascular catecholamine response (10). It is highly uncertain, however, whether prevention of dilutional acidosis has an effect on clinically relevant outcomes in patients who need fluid resuscitation for shock. Moreover, balanced solutions contain different buffers, such as lactate, acetate, or gluconate, which all could have side-effects when infused in large amounts (11).

We performed a meta-analysis of published randomized controlled trials (RCTs) comparing fluid resuscitation with balanced solutions versus isotonic saline in patients either in the operation room or in the intensive care unit (ICU). We hypothesized that fluid resuscitation with balanced solutions is associated with higher in-hospital survival, less development of acute kidney injury (AKI) and less need for renal replacement therapy (RRT). We also determined whether fluid resuscitation with balanced solutions was associated with changes in serum chloride, and arterial pH.

Methods

Search strategy

Studies were identified through an electronic search in PubMed (1966 to February 2016) and CENTRAL (the Cochrane Library to February 2016) using a sensitive search strategy incorporating keywords as well as Medical Subject Headings. Details of the search strategy are reported in Supplementary files and *Table S1*. All articles identified by the search were scanned for relevancy by title and abstract. For potentially relevant articles the full text was obtained for review; for these articles, all references were inspected and potentially relevant titles were hand searched. The search had no limitations.

Selection of studies

We restricted the search to (I) RCTs; (II) comparing fluid resuscitation with a balanced solution versus isotonic saline; (III) in adult patients (age >18 years) in (IV) operation room or ICUs. We excluded observational studies, studies conducted exclusively in emergency departments (EDs), studies in pregnant, and trials in which fluid resuscitation with a balanced solution was compared with resuscitation with a colloid solution. Colloid infusion before start of a trial was not a reason for exclusion. Two independent researchers (A.S.N. and R.B.K.) performed the search and results were entered into a database. Wherever these researchers disagreed, this was settled by discussion or by including a third researcher (I.M.L.). The Cochrane Risk of Bias Tool was used to assess the quality of the studies.

Endpoints

The primary endpoint was in-hospital mortality at longest follow-up, which was defined as death during hospital stay. Secondary outcomes were development of AKI, need for RRT, ICU—and hospital length of hospital, and the incidence of metabolic acidosis and changes in plasma chloride levels are described.

Statistical analysis

We expressed pooled dichotomous data and pooled continuous effect measures as odds ratio (OR) or standardized mean difference (SMD) with a 95% confidence intervals (95% CI). A random-effects model was used for all analyses. Trials in ICUs were separated from trials in operation room, as the prognosis is very different in these patient categories, and different outcomes with respect to the primary endpoint, in-hospital mortality, were suspected.

The homogeneity assumption was measured by the I^2, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. I^2 was calculated from basic results obtained from a typical meta-analysis as $I^2=100\% \times (Q - \mathrm{df})/Q$, where Q is the Cochran heterogeneity statistic. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. All analyses were conducted stratified according to location of patients (ICU *vs.* operation room).

Parametric variables were presented as the mean ± SD and non-parametric variables were presented as the median (interquartile range). All analyses were conducted with

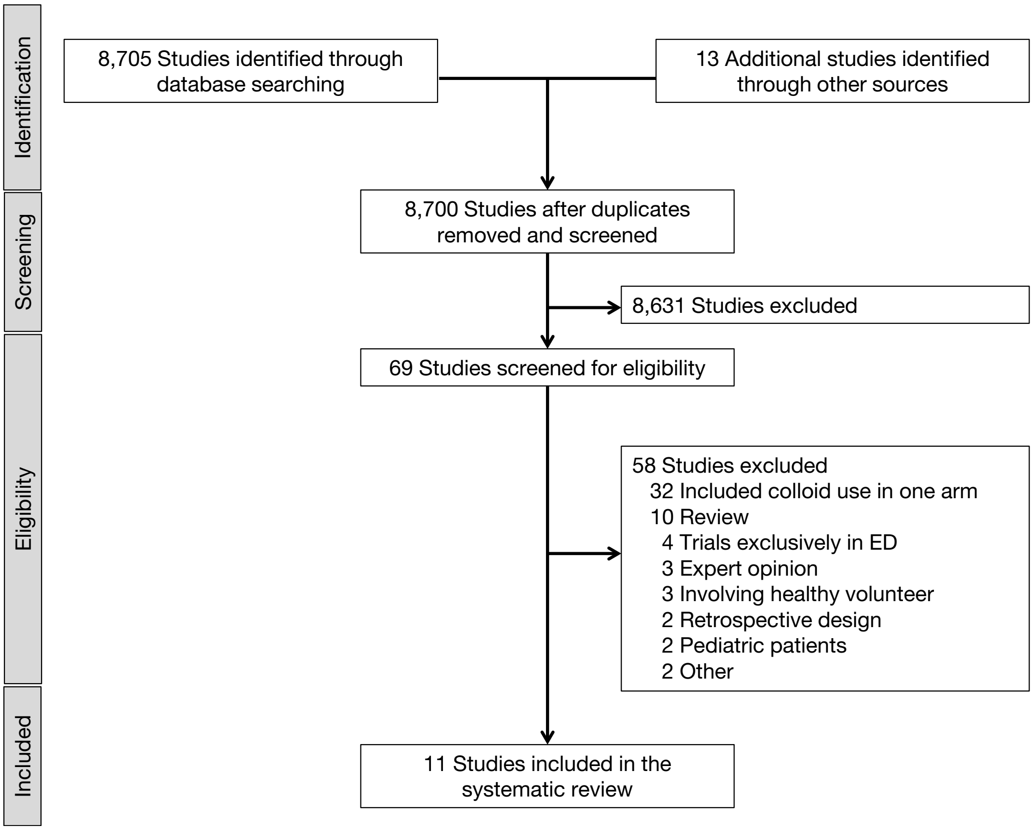

Figure 1 Flowchart of the search strategy. ED, emergency department.

Review Manager v.5.1.1, SPSS v.20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corporation) or R v.2.12.0 (R Foundation for Statistical Computing, Vienna, Austria). For all analyses two-sided P<0.05 were considered significant.

Results

Search results

The initial search yielded 8,718 articles (940 from MEDLINE, and 1,258 from CENTRAL). After removing duplicates, the abstracts of 8,700 articles were evaluated. We excluded 8,631 articles because they did not meet the inclusion criteria. Subsequently, the full text of the remaining 69 articles was obtained. Fifty-eight articles were excluded after full text review due to following reasons: included colloid or other solutions in one of the trial arms (n=32); reviews (n=10); trials conducted exclusively in EDs (n=4); not an RCT (n=5); involving healthy volunteers (n=3), RCT in pediatric patients (n=2), RCT in a non–human setting (n=1) and article retracted (n=1). Finally, 11 RCTs (2,703 participants) were included in the final analysis (*Figure 1*) (12-22). The composition of the balanced solutions tested in each RCT is shown in *Table S2*.

Description of studies

The RCTs were published between 1994 and 2015 and included operation room patients in eight and ICU patients in three RCTs (*Table 1*). The methodological quality of the RCTs is shown in *Figure S1*. In all trials the random sequence generation was described and only in two trials the description of the allocation concealment was unclear (*Figure S1*). Regarding blinding of participants, personnel and assessments, four trials were considered at high risk of bias (*Figure S1*).

All RCTs used isotonic saline for fluid resuscitation in the control arm. Infused amounts of fluids and duration of fluid infusions are shown in *Table S3*. In operation room patients, the total amount of fluids used for resuscitation varied from 1.5 to 7.0 liters; in ICU patients the total amount of fluids

Table 1 Characteristics of the included randomized controlled trials

First author, year	Country	Design	Patients	Setting	Balanced solution		Non-balanced solution		Endpoint
					N	Solution	N	Solution	
McFarlane, 1994	UK	RCT	HBP surgery	Operation room	15	Plasma-Lyte® 148	15	Isotonic saline	Acid-base and biochemistry
Scheingraber, 1999	Germany	RCT	Gynecological surgery	Operation room	12	Ringer's lactate	12	Isotonic saline	Renal function
Waters, 2001	USA	RCT/DB	AAA surgery	Operation room	33	Ringer's lactate	33	Isotonic saline	Acid-base, biochemistry and clinical outcome
O'Malley, 2005	USA	RCT/DB	Kidney transplantation	Operation room	25	Ringer's lactate	26	Isotonic saline	Biochemistry and renal function
Hadimioglu, 2008	Turkey	RCT/DB	Kidney transplantation	Operation room	30 30	Plasma-Lyte® 148 Ringer's lactate	30	Isotonic saline	Acid-base, biochemistry and renal function
Khajavi, 2008	Iran	RCT/DB	Kidney transplantation	Operation room	26	Ringer's lactate	26	Isotonic saline	Renal function
Wu, 2011	USA	RCT	Acute pancreatitis	ICU	19	Ringer's lactate	21	Isotonic saline	Clinical outcomes, renal function
Kim, 2013	Korea	RCT/DB	Kidney transplantation	Operation room	30	Plasma-Lyte® A	30	Isotonic saline	Acid-base, biochemistry and renal function
Potura, 2015	Switzerland	RCT	Kidney transplantation	Operation room	72	Elomel Isoton®	76	Isotonic saline	Acid-base, biochemistry and renal function
Young, 2014	USA	RCT/DB	Trauma patients	ICU	22	Plasma-Lyte® A	24	Isotonic saline	Acid-base, biochemistry and clinical outcome
Young, 2015	New Zealand	RCT/DB	ICU patients	ICU	1,152	Plasma-Lyte® 148	1,110	Isotonic saline	Renal function and clinical outcomes

RCT, randomized controlled trial; DB, database; HBP, high blood pressure; ICU, intensive care unit.

Table 2 Balanced *vs.* non-balanced fluid strategy and in-hospital mortality, ICU- and hospital-length of stay, development of AKI and RRT in operation room patients

First author, year, endpoint	Patients, n	Patients with study end point, by fluid strategy, n/n or mean (SD)		Odds ratio or std. mean difference (95% CI)	P value	I^2	P value
		Balanced	Non-balanced				
In-hospital mortality							
Waters, 2001	66	1/33	1/33	1.00 (0.06 to 16.69)			
Summary	66	1/33	1/33	1.00 (0.06 to 16.69)	1.00	NA	NA
ICU length of stay							
Waters, 2001	66	4.1 (7.6)	2.8 (3.8)	0.21 (–0.27 to 0.77)			
Summary	66			0.21 (–0.27 to 0.77)	0.39	NA	NA
Hospital length of stay							
Waters, 2001	66	10.1 (8.3)	8.9 (4.7)	0.18 (–0.31 to 0.66)			
Summary	66			0.18 (–0.31 to 0.66)	0.48	NA	NA
Acute kidney injury							
Waters, 2001[a]	66	4/33	5/33	0.77 (0.19 to 3.18)			
Summary	66	4/33	5/33	0.77 (0.19 to 3.18)	0.72	NA	NA
Renal replacement therapy							
O'Malley, 2005[b]	51	1/25	2/26	0.50 (0.04 to 5.89)			
Hadimioglu, 2008[b]	90	3/60	3/30	0.47 (0.09 to 2.50)			
Potura, 2015[b]	148	19/72	19/76	1.08 (0.51 to 2.25)			
Summary	289	23/157	24/132	0.90 (0.47 to 1.72)	0.75	0%	0.60

[a], did not describe the definition of AKI; [b], did not describe how RRT was indicated. ICU, intensive care unit; AKI, acute kidney injury; RRT, renal replacement therapy; NA, not applicable.

used for resuscitation varied from 2.6 to 10.3 liters.

Primary outcome

In operation room patients, one out of 33 patients (3.0%) receiving balanced solutions and one out of 33 patients (3.0%) receiving isotonic saline died during hospital stay (OR, 1.00; 95% CI, 0.06–16.69; P=1.00; one study included in the analysis) (*Table 2*). In ICU patients, 90 out of 1,193 patients (7.5%) receiving balanced solutions and 99 out of 1,155 patients (8.6%) receiving isotonic saline died during hospital stay (OR, 0.87; 95% CI, 0.65–1.17; P=0.36; three studies included in the analysis) (*Table 3*). There was no sign of heterogeneity (I^2=0%).

Secondary outcomes

In operation room patients, there were no differences in subsequent ICU or hospital length of stay for patients receiving balanced solution compared to isotonic saline (one study included in the analysis, *Table 2*). Available information was not sufficient for a meta-analysis of ICU and hospital length of stay in ICU patients.

In operation room patients, four out of 33 patients (12.1%) receiving balanced solutions and five out of 33 patients (15.1%) receiving isotonic saline developed AKI during hospital stay (OR, 0.77; 95% CI, 0.19–3.18; P=0.72; one study included in the analysis) (*Table 2*). In ICU patients, 106 out of 1,108 patients (9.6%) receiving balanced solutions and 102 out of 1,070 patients (9.5%) receiving isotonic saline developed AKI during hospital stay (OR, 1.00; 95% CI, 0.75–1.34; P=0.97; three studies included in the analysis) (*Table 3*). There were no differences in the need of RRT, neither in operation room patients (three studies included in the analysis, *Table 2*) nor in ICU patients (one study included in the analysis, *Table 3*). There was no

Table 3 Balanced *vs.* non-balanced fluid strategy and in-hospital mortality, ICU- and hospital-length of stay, development of AKI and RRT in ICU patients

First author, year, endpoint	Patients, n	Patients with study end point, by fluid strategy, n/n or mean (SD)		Odds ratio or std. mean difference (95% CI)	P value	I^2	P value
		Balanced	Non-balanced				
In-hospital mortality							
Wu, 2011	40	0/19	0/21	Not estimable			
Young, 2014	46	3/22	4/24	0.79 (0.16 to 4.00)			
Young, 2015	2,262	87/1,152	95/1,110	0.87 (0.64 to 1.18)			
Summary	2,348	90/1,193	99/1,155	0.87 (0.65 to 1.17)	0.36	0%	0.91
Acute kidney injury							
Wu, 2011[a]	40	1/19	2/21	0.53 (0.04 to 6.34)			
Young, 2014[b]	46	3/22	6/24	0.47 (0.10 to 2.18)			
Young, 2015[c]	2,092	102/1,067	94/1,025	1.05 (0.78 to 1.41)			
Summary	2,178	106/1,108	102/1,070	1.00 (0.75 to 1.34)	0.97	0%	0.47
Renal replacement therapy							
Wu, 2011[d]	40	1/19	2/21	0.53 (0.04 to 6.34)			
Young, 2015[d]	2,262	38/1,152	38/1,110	0.96 (0.61 to 1.52)			
Summary	2,302	39/1,171	40/1,131	0.94 (0.60 to 1.48)	0.80	0%	0.64

[a], did not describe the definition of AKI; [b], AKI defined using the AKIN criteria; [c], AKI defined using the RIFLE criteria; [d], did not describe how RRT was indicated. ICU, intensive care unit; AKI, acute kidney injury; RRT, renal replacement therapy.

sign of heterogeneity (I^2=0%).

Metabolic status

The incidence of metabolic acidosis, as reported in six RCTs, was not different between the two randomized groups, neither in operation room nor in ICU patients (*Tables 4,5*). Changes in arterial pH after fluid resuscitation were also similar between the two types of fluids, both in operation room and ICU patients (*Tables 4,5*). In both patient groups there was a larger increase in the chloride levels after fluid resuscitation with isotonic saline compared to balanced solutions (*Tables 4,5*).

Discussion

The present meta-analysis of RCTs comparing fluid resuscitation with balanced solutions with isotonic saline for shock treatment did not find a difference in in-hospital mortality, occurrence of AKI or need for RRT. Compared to resuscitation with isotonic saline, resuscitation with balanced solutions was associated with a smaller increase in the chloride levels. These effects were not different between operation room and ICU patients. One silent finding was that the number of high quality RCTs published on this topic is surprisingly low, seen the frequency with which these fluids are administered in operation room and ICU patients.

The strength of this meta-analysis is the approach of a systematic review and meta-analysis method by only including RCTs. Retrospective or observational studies (23) were excluded, as such preventing the risk for bias. Also studies that compared balanced solutions along with colloids and gelatins (24,25). The RCTs used in the meta-analysis were all of high quality, and included operation room as well as ICU patients allowing comparisons in the two patient groups those were most often subjected to fluid resuscitation.

Intravenous fluids are by far the most frequently administered drugs in the operation room and ICUs. Compositions of intravenous fluids have been and remain

Table 4 Balanced *vs.* non-balanced fluid strategy and incidence of hyperchloremic metabolic acidosis, change in serum pH, and chloride levels in operation room patients

First author, year, endpoint	Patients, n	Patients with study end point, by fluid strategy, n/n or mean (SD)		Odds ratio or std. mean difference (95% CI)	P value	I^2	P value
		Balanced	Non-balanced				
Incidence of hyperchloremic metabolic acidosis							
O'Malley, 2005	51	0/25	8/26	0.04 (0.00 to 0.79)			
Hadimioglu, 2008	60	0/30	0/30	Not estimable			
Khajavi, 2008	52	0/26	2/26	0.18 (0.01 to 4.05)			
Potura, 2015	148	3/72	5/76	0.62 (0.14 to 2.68)			
Summary	311	3/153	15/158	0.25 (0.05 to 1.30)	0.10	32%	0.23
Change in serum pH							
Waters, 2001	66	−0.02 (0.00)	−0.08 (0.03)	Not estimable			
O'Malley, 2005	51	0.01 (0.01)	−0.11 (0.02)	7.43 (5.83 to 9.03)			
Hadimioglu, 2008	90	0.00 (0.01)	−0.08 (0.45)	0.31 (−0.13 to 0.75)			
Khajavi, 2008	52	−0.01 (0.07)	−0.06 (0.05)	−1.13 (−1.72 to −0.52)			
Kim, 2013	60	−0.11 (0.03)	−0.06 (0.02)	−1.94 (−2.56 to −0.32)			
Potura, 2015	148	−0.05 (0.01)	−0.06 (0.02)	0.62 (0.29 to 0.95)			
Summary	467			0.83 (−0.66 to 0.95)	0.27	97%	0.00
Change in serum chloride							
McFarlane, 1994	30	0.6 (0.2)	6.9 (2.3)	−3.34 (−4.50 to −2.19)			
Scheingraber, 1999	24	2.0 (0.5)	11.0 (0.0)	Not estimable			
Waters, 2001	66	2.0 (1.0)	9.0 (3.0)	−3.09 (−3.82 to −2.37)			
Hadimioglu, 2008	90	2.5 (1.0)	21.2 (0.5)	−24.37 (−24.59 to −18.50)			
Kim, 2013	60	−0.9 (0.0)	4.0 (0.0)	Not estimable			
Potura, 2015	148	2.0 (1.9)	4.0 (1.9)	−1.05 (−1.39 to −0.70)			
Summary	418			−6.48 (−9.74 to −3.23)	0.00	98%	0.00

to be a matter of debate in both patient populations. Based on the non-physiological composition of 'normal saline', the interest to find a fluid that will provide the optimal composition has moved from synthetic colloid solutions to 'more physiologic' balanced solutions. The hypothetical benefit of resuscitation with balanced solutions is prevention of dilutional acidosis. By definition, balanced fluids are those that contain an electrolyte constitution that more closely resemble plasma concentrations; they impose a lower chloride-load but contain buffering agents. In experimental models of sepsis, occurrence of hyperchloremia is associated with an increased pro-inflammatory state (6,7), suggesting an immunomodulatory effect. In healthy volunteers, hyperchloremia is associated with a decrease in mean renal artery flow velocity and renal cortical tissue perfusion (26), and an increased time to urination and decreased urine production (26,27). Observational studies in ICU patients suggest an increased mortality in association with hyperchloremia (28), coagulopathy (29), decreased organ perfusion (30) and gastro-intestinal symptoms (8), as well as increased need for transfusion of blood products (24,31,32). Thus, balanced solutions could have a strong potential to affect outcome of patients with shock, who are frequently suffering from a pro-inflammatory and pro-coagulant state.

The results of the present systematic review and meta-

Table 5 Balanced *vs.* non-balanced fluid strategy and incidence of hyperchloremic metabolic acidosis, change in serum pH, and chloride levels in ICU patients

First author, year, endpoint	Patients, n	Patients with study end point, by fluid strategy, n/n or mean (SD)		Odds ratio or std. mean difference (95% CI)	P value	I^2	P value
		Balanced	Non-balanced				
Incidence of hyperchloremic metabolic acidosis							
Young, 2014	46	1/22	0/24	3.42 (0.13 to 88.40)			
Young, 2015	2,262	13/1,152	9/1,110	1.40 (0.59 to 3.28)			
Summary	2,308	14/1,174	9/1,134	1.48 (0.65 to 3.38)	0.35	0%	0.60
Change in serum pH							
Young, 2014	46	0.12 (0.06)	0.11 (0.02)	0.22 (−0.27 to 0.71)			
Summary	46			0.22 (−0.27 to 0.71)	0.37	NA	NA
Change in serum chloride							
Young, 2014	46	−2.0 (0.1)	4.0 (4.0)	−2.08 (−2.69 to −1.47)			
Summary	46			−2.08 (−2.69 to −1.47)	0.00	NA	NA

ICU, intensive care unit; NA, not applicable.

analysis add to our understanding of the role of balanced solutions in fluid resuscitation by suggesting that major outcome measures do not differ between following fluid resuscitation with balanced and isotonic saline solutions, both in operation room and ICU patients. More RCTs are needed to show whether resuscitation with balanced or isotonic solutions affects important clinical endpoints before a recommendation for one type of fluid can be made. Actually, from the results of this systematic review and meta-analysis one could conclude that currently evidence insufficiently supports the use of balanced over isotonic saline for fluid resuscitation to improve outcome, both in operation room and ICU patients.

The findings of the meta-analysis seem in contrast, at least in part with findings in previous studies reporting clinical benefit of chloride-poor or balanced solutions versus isotonic saline in operation room and ICU patients. One retrospective observational study in operation room patients undergoing major surgery evaluated the effect of balanced versus non-balanced fluid showed no differences in mortality, but there was a 5-fold increase in the need for RRT in patients resuscitated with isotonic saline (33). This study, however, had several limitations, including differences in matched cohort baseline characteristics and increased use of balanced fluids in teaching hospitals possibly indicating differences in standard of care. A prospective observational study in 1,500 ICU patients also did not show an association between use of balanced solutions and mortality, but did find a marked decrease of AKI with use of balanced solutions and need for RRT (34). In this study, use of colloids was not excluded, which could have affected outcomes. One retrospective observational study found an association between use of balanced fluids and in-hospital death in ICU patients with sepsis, though no differences in the occurrence of renal failure or need for RRT (35). Notably, in this study less than 5% of patients actually received balanced solutions, and over 20% of patients received colloids.

Fluid resuscitation with balanced solutions could come with important side-effects. All balanced solutions to date contain buffering agents, like lactate, acetate, citrate or malate. These all are converted in the liver. Over-use of these buffers might result in metabolic alkalosis, or in the setting of either liver failure or shock, conversion could be severely impaired (11), e.g., leading to hyperlactatemia. Other side effects include increased nitric oxide production due to acetate, which could lead to hypotension and cardiac dysfunction (36). Finally, some balanced solutions contain magnesium which can induce bradycardia and increase peripheral vascular resistance leading to decrease in microcirculation and worsening of organ ischemia (37). Most of these side-effects were not reported in the trials analyzed, which is not surprising as they were not systematically looked for.

This systematic review shows that the number of high quality RCTs published on this topic is low, which is surprising seen the fact that these fluids are massively described and used in daily clinical practice worldwide. The operation room and ICU communities need to perform well-powered studies, preferably well-designed RCTs, which not only focus on patient-centered endpoints such as mortality, length of stay in ICU and hospital, development of AKI and need for RRT, but also the potential side-effects summarized above.

Our meta-analysis also knows several limitations. First of all, the analysis was limited due to the low number of RCTs that fulfilled all in- and exclusion criteria. The fact that practically all outcomes were only reported by some eligible trials is another limitation. Indeed, unreported outcomes could lead to overestimation of effects in meta-analyses (38). Secondly, five out of eight RCTs in the operation room were performed in patients undergoing renal transplantation who are high risk for development of dilutional acidosis. Furthermore, we were limited by the fact that the kidney injury scoring was not reported in seven RCTs and could not be used in two out of the four remaining RCTs because they were performed before the current scoring system was implemented. Need for RRT was easier to capture, however, but we may have had insufficient power to find a difference. Also, the results of the meta-analysis were highly influenced by one single large RCT (22). Finally, the incidence of clinical relevant outcomes, as used in this meta-analysis was very low in operation room patients, reducing its power.

Conclusions

The present meta-analysis does not support the use of balanced solutions for fluid resuscitation, neither in ICU nor in operation room patients.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Serpa Neto A, Martin Loeches I, Klanderman RB, Freitas Silva R, Gama de Abreu M, Pelosi P, Schultz MJ; for the PROVE Network Investigators. Balanced versus isotonic saline resuscitation—a systematic review and meta-analysis of randomized controlled trials in operation rooms and intensive care units. Ann Transl Med 2017;5(16):323. doi: 10.21037/atm.2017.07.38

Supplementary

Search strategy

1. randomized controlled trial [ptyp]
2. controlled clinical trial [ptyp]
3. randomized [Title/Abstract]
4. placebo [Title/Abstract]
5. drug therapy [Subheading]
6. randomly [Title/Abstract]
7. trial [Title/Abstract]
8. groups [Title/Abstract]
9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10. animals [mh] NOT humans [mh]
11. #9 NOT #10
12. (fluid resuscitation)[Title/Abstract] OR fluid therapy[Title/Abstract])
13. ("crystalloid solutions" [Supplementary Concept]) OR ("Isotonic Solutions"[Mesh])
14. ("Balance*"[Title/Abstract] OR "buffer*"[Title/Abstract]) AND ("saline"[Title/Abstract] OR "solution*"[Title/Abstract] OR "crystalloid*"[Title/Abstract] OR "Fluid*"[Title/Abstract])
15. (“chloride*”[Title/Abstract]) AND (“content”[Title/Abstract] OR “poor”[Title/Abstract] OR “rich”[Title/Abstract] OR “high”[Title/Abstract] OR “low”[Title/Abstract] OR “liberal”[Title/Abstract] OR “restrict*”[Title/Abstract])
16. (“Plasmalyt*”[Title/Abstract] OR “Plasma-lyte” [Title/Abstract])
17. “Sterofundin” [Title/Abstract] OR “Ringerfundin” [Title/Abstract] OR “isofundin” [Title/Abstract]

(“Ringer*”[Title/Abstract] AND (“solution*”[Title/Abstract] OR "Lactate*"[Title/Abstract] OR “Acetate*”[Title/Abstract]))

(“Hartmann*”[Title/Abstract] AND (“solution*” [Title/Abstract])

#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

#11 AND #20

Table S1 Research question using PICO structure

Population
Adult surgical and non-surgical patients requiring volume replacement
Intervention
Balanced solutions (e.g., Plasma-Lyte®, Ringer Lactated)
Comparator
Non-balanced solutions (i.e., isotonic saline)
Outcomes
Primary outcome
Incidence of in-hospital mortality
Secondary outcomes
(I) Incidence of patients with acute kidney injury (defined according to RIFLE categories of GFR and urine output and the use of renal replacement therapy). It should be noted that the actual measurement of this outcome will be somewhat dictated by what is reported in the individual trials
(II) Incidence of use of renal replacement therapy
(III) Intensive care unit and hospital length of stay
(IV) Changes in plasma chloride levels
Study design
Randomized controlled trials.

Table S2 Composition of the fluid solutions tested in the randomized controlled trials

Solution	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Lactate (mmol/L)	Calcium (mmol/L)	Magnesium (mmol/L)	Bicarbonate (mmol/L)	pH
Normal saline	154	0.0	154	0.0	0	0.0	0	5.00
Ringer's lactate	130	4.0	115	28.0	3	0.0	0	6.50
Plasma-Lyte® 148	140	5.0	98	0.0	0	1.5	27 (acetate); 23 (gluconate)	5.50
Plasma-Lyte® A	140	5.0	98	0.0	0	1.5	27 (acetate); 23 (gluconate)	7.40
Elomel Isoton®	140	5.0	108	0.0	2.5	1.5	45 (acetate)	5.60–6.40
Ringer's solution	147	4.0	155.5	0.0	2.25	0.0	0	5.00–7.50
Blood plasma	134–146	3.4–5.0	98–108	2.0–9.0	2.25–2.65	0.7–1.1	22–32	7.36–7.44

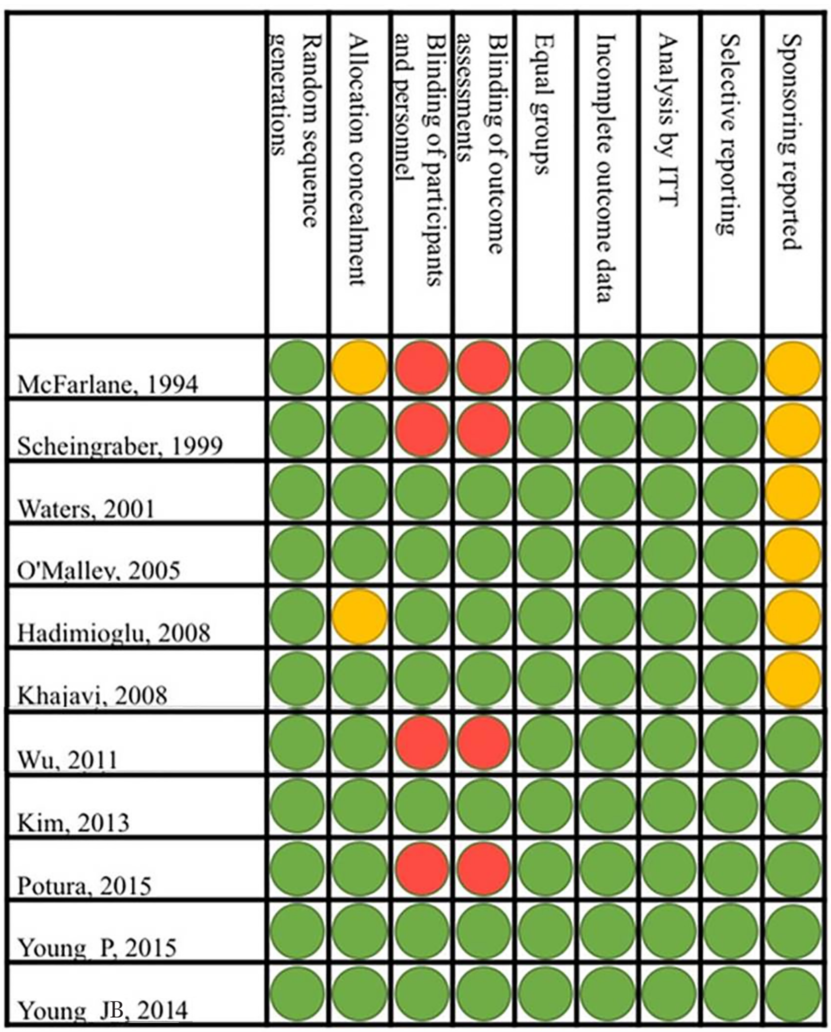

Figure S1 Methodological quality of the included trials.

Table S3 Pre-specified quantity of fluid and actual quantity used in each randomized controlled trial

Study	Pre-specified by protocol	Balanced solution actual quantity infused	Duration of infusion (min)	Isotonic saline pre-specified by protocol	Actual quantity infused	Duration of infusion (min)
McFarlane (12)	15 mL/kg/h	15.1±3.5 mL/kg/h	197±56	15 mL/kg/h	14.6±4.1 mL/kg/h	219±77
Scheingraber (13)	30 mL/kg/h	33.5±9 mL/kg/h	138±20	30 mL/kg/h	35.5±7 mL/kg /h	135±23
Waters (14)	CVP within 10% of baseline	6,871±1,628 mL	–	CVP within 10% of baseline	7,000±2,590	–
O'Malley (15)	–	5,600±1,400 mL	336±78	–	6,100±1,200 mL	336±66
Hadimioglu (16)	20–30 mL/kg/h	2,770±820 mL 2,756±800 mL	118±10 118±17	20–30 mL/kg/h	2,868±780 mL	119±13
Khajavi (17)	CVP between 10–15 mmHg	–	–	CVP between 10–15 mmHg	–	–
Wu (18)	'Goal-directed therapy'	–	1,440	'Goal-directed therapy'	–	1,440
Kim (19)	CVP between 12–15 mmHg	3,083±1,082 mL	302±63	CVP between 12–15 mmHg	3,249±891 mL	305±49
Potura (20)	2 mL/kg h after 4 mL/kg/h	2,500±777 mL	–	2 mL/kg/h after 4 mL/kg/h	2,625±814 mL	–
Young (21)	–	10,300±6,500 mL	1,440	–	9,000±5,500 mL	1,440
Young (22)	According to attending physician	–	–	According to attending physician	–	–

CVP, central venous pressure.