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Barea Mendoza JA, Antequera AM, Plana MN, Chico-Fernández M, Muriel A, Sáez I, Estrada-Lorenzo JM.
Buffered solutions versus isotonic saline for resuscitation in non-surgical critically ill adults and children.
Cochrane Database of Systematic Reviews 2016, Issue 6. Art. No.: CD012247.
DOI: 10.1002/14651858.CD012247.

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Buffered solutions versus isotonic saline for resuscitation in non-surgical critically ill adults and children

Jesus A Barea Mendoza¹, Alba M Antequera², Maria N Plana³, Mario Chico-Fernández¹, Alfonso Muriel⁴, Ignacio Sáez¹, José M Estrada-Lorenzo⁵

¹Intensive Care Department, 12 de Octubre Hospital, Madrid, Spain. ²Internal Medicine Department, La Princesa Hospital, Madrid, Spain. ³Universidad Francisco de Vitoria (UFV) Madrid, Madrid, Spain. ⁴Clinical Biostatistics Unit, Ramón y Cajal Hospital (IRYCIS), CIBER Epidemiology and Public Health (CIBERESP), Madrid, Spain. ⁵Medical Library, 12 de Octubre Hospital, Madrid, Spain

Contact address: Jesus A Barea Mendoza, Intensive Care Department, 12 de Octubre Hospital, Avda de Cordoba, s/n, 28041, Madrid, Spain. jbareamendoza@gmail.com, jesusabelardo.barea@salud.madrid.org.

Editorial group: Cochrane Emergency and Critical Care Group.

Publication status and date: Edited (no change to conclusions), published in Issue 1, 2019.

Citation: Barea Mendoza JA, Antequera AM, Plana MN, Chico-Fernández M, Muriel A, Sáez I, Estrada-Lorenzo JM. Buffered solutions versus isotonic saline for resuscitation in non-surgical critically ill adults and children. *Cochrane Database of Systematic Reviews* 2016, Issue 6. Art. No.: CD012247. DOI: 10.1002/14651858.CD012247.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess effects of buffered solutions versus isotonic saline for resuscitation in non-surgical critically ill adults and children.

BACKGROUND

Description of the condition

Intravenous fluid therapy is probably the intervention provided most frequently for critically ill patients (Myburgh 2015). More than a third of all hospitalized patients are given intravenous fluid therapy (Finfer 2010). It is estimated that every year, 200 million litres of intravenous fluids is used in the USA (Young 2014), as well as 10 million litres of isotonic saline in the UK (Awad 2008). Intravenous fluid preparations differ in their physiochemical properties. The ideal intravenous fluid should keep electrolytes and pH at physiological levels and should have the ability to expand intravascular volume (Myburgh 2013). For many clinical scenarios, such as sepsis, acute pancreatitis and severe trauma, intravenous fluid therapy serves as the cornerstone of treatment.

Available options for fluid therapy vary widely in terms of fluid volume, timing and choice of solution. However, no standard care intravenous fluid therapy has been universally accepted (Finfer 2010; Singer 2012). The cost of different intravenous solutions has been estimated at three to 100 times greater than the cost of isotonic saline (Lyu 2014). Several medical societies and authors have developed consensus papers and evidence-based guidelines intended to improve decisions about fluids and related outcomes (Garnacho-Montero 2015; NICE 2013; Raghunathan 2014b; Reinhart 2012). Other guidelines more focused on critical illness have provided recommendations concerning fluid therapy (Dellinger 2013; Maraví 2014).

Fluid therapy solutions are classified as colloid or crystalloid solutions. Colloids are solutions composed of large molecules dispersed throughout fluid. In theory, they cannot cross the healthy semi permeable endothelial layer owing to their large molecular

size, but this is not a criterion to be considered colloids. Colloids have been described as more effective than crystalloids in increasing intravascular volume (Trof 2010).

However, according to two Cochrane systematic reviews, colloids offer no benefit over crystalloids and may even increase risks of renal failure and death (Mutter 2013; Perel 2013). Further, studies addressing glycocalyx function during critical illness have provided some explanation for possible detrimental effects of colloids. New insight into the Starling principle (Starling 1896) suggests that the glycocalyx is the main determining factor in transcapillary flow. In disease states, the integrity of the glycocalyx may be compromised, and this translates to its greater permeability and a rise in the oncotic pressure gradient, causing interstitial oedema (Levick 2010; Woodcock 2012). Accordingly, recent evidence does not support the use of colloids for resuscitation in critically ill patients (Hartog 2014; Reinhart 2012).

Isotonic saline is a widely used crystalloid solution, yet it causes hyperchloraemic acidosis with significant consequences for patients identified in several observational studies (Raghunathan 2014a; Shaw 2014; Yunos 2014). As safer crystalloids, buffered solutions have been assessed for their resuscitation capacity. According to a Cochrane review of the safety and efficacy of buffered fluids in adult patients undergoing elective surgery, those who received buffered solutions did not develop hyperchloraemic acidosis (Burdett 2012). In another systematic review of elective surgery and critical care, high-chloride fluids were associated with greater risk of acute kidney; this particular review provided little evidence of effects on mortality (Krajewski 2015). Elective surgical patients have characteristics different from those of critically ill patients. Fluid therapy prescribed for non-surgical patients is targeted more at multiple organ dysfunction syndrome. This means that conclusions of reviews that have examined intravenous fluid therapy in elective surgical patients cannot necessarily be transferred to critically ill patients (Burdett 2012).

In summary, according to recent evidence, use of colloid solutions in critically ill patients for resuscitation purposes generally is not recommended, and the benefits of buffered solutions or isotonic saline in this patient subset remain unclear.

Description of the intervention

Crystalloids are aqueous solutions of ions that show different properties according to their ion concentrations (Appendix 1). Because of its low cost, user experience and general availability, isotonic saline is the most commonly used intravenous fluid (Awad 2008). Use of terms such as *normal* or *physiological saline* is not recommended by the authors of this review because, although isotonic saline contains sodium and chloride in equal concentrations, it contains higher than physiological levels. The terms *normal* and *physiological* refer to historical issues rather than to chemical properties (Awad 2008). Hence, in this current review, we will use the term *isotonic saline*.

Other crystalloid formulations, called *balanced* or *buffered solutions*, differ from isotonic saline in terms of three properties: lower sodium and chloride contents, bringing them closer to normal plasma levels; the presence of other ions such as potassium, calcium or magnesium, which could have effects on factors such as potassium or lactate levels, or could play a role in liver disease (Orbegozo 2014); and finally, their contents of anions such as lactate, acetate and gluconate, which are metabolized to bicarbonate by tissue cells and may exert an additional buffering effect.

How the intervention might work

Data from experimental animal (Kellum 1998) and human studies (Chowdhury 2012) suggest that infusion of isotonic saline may induce greater hyperchloraemic acidosis and interstitial oedema than are associated with use of intravenous buffered solutions. Experimental studies have shown that hyperchloraemic acidosis increases the risk of worsening renal function through effects such as renal vasoconstriction, low renal perfusion pressure and low glomerular filtration rate (Schnermann 1976; Wilcox 1983). Effects of acidosis on the immune system have been described in a rat model (Kellum 2006). Further, changes in systemic inflammation response have been linked to acidosis in humans (Wu 2011). In a before-and-after trial, a chloride-restrictive strategy was associated with significant reduction in the incidence of acute kidney injury and the need for renal replacement therapy (RRT) in adult intensive care patients (Yunos 2012; Yunos 2014). In a recent observational study, hyperchloraemic acidosis was associated with increased mortality among critically ill patients (Raghunathan 2014a). The effect observed could be independent of the fluid volume administered and may be more closely related to the chloride load (Shaw 2014). These data suggest that buffered solutions, with their lower chloride concentrations than isotonic saline, may reduce the incidence of hyperchloraemic acidosis, thus decreasing the risk of patient-centred outcomes such as renal failure, need for RRT and mortality (McCluskey 2013; Raghunathan 2014a).

Why it is important to do this review

Several observational studies in the critical care setting have reported an association between hyperchloraemic acidosis and relevant outcomes such as acute renal injury and mortality (Raghunathan 2014a; Shaw 2014; Yunos 2014).

A recent Cochrane systematic review concluded that buffered intravenous fluids reduce the incidence of hyperchloraemia and metabolic acidosis in elective surgery (Burdett 2012). However, trials reviewed were not adequately powered to permit conclusions about renal failure or mortality and did not include critically ill patients.

Several recent randomized trials have examined the effects of buffered solutions in critically ill patients. In one such study, faster

pH normalization was observed among severely dehydrated participants receiving buffered fluid therapy (Cieza 2013). Two randomized controlled trials conducted in trauma patients described a reduction in the incidence of hyperchloraemic acidosis without a rise in intracranial pressure (Roquilly 2013; Young 2014). Other trials have explored the potential benefits of buffered solutions in clinical settings such as diabetes (Van Zyl 2012), acute pancreatitis (Wu 2011; Zhao 2013), dengue (Wills 2005) and doxylamine-induced rhabdomyolysis (Cho 2007). However, in the recent (0.9% Saline versus Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy) *SPLIT* study which included 2278 critical care participants, there were no differences between isotonic saline and Plasma-Lyte 148 (Young 2015).

The present systematic review will identify and synthesize all available evidence on the efficacy and safety of isotonic buffered solutions versus isotonic saline when used in critically ill patients. On the basis of wide use of this therapy and the amount of solution administered, minor effects of the intervention may have an impact on clinical outcomes.

OBJECTIVES

To assess effects of buffered solutions versus isotonic saline for resuscitation in non-surgical critically ill adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) of parallel or cross-over design, regardless of language of publication. We will exclude studies performed in persons undergoing elective surgery. We will consider unpublished studies and abstracts, provided adequate information on methods and results is provided.

Types of participants

We will include studies on participants with critical illness (including trauma, burns or emergency surgery during critical illness) who require intravenous fluid therapy. We will include studies of adults and children, and we will explore the effects of age in a subgroup analysis ([Subgroup analysis and investigation of heterogeneity](#)).

Types of interventions

Interventions considered will include use of intravenous buffered solutions containing bicarbonate or its precursors ([Appendix 1](#)) versus intravenous isotonic saline as control. We will consider all uses of fluids in a critical care setting of resuscitation or maintenance. We will require that included fluids are isotonic (osmolality 250 to 350 mmol/L).

To minimize confounding factors, we will not consider studies with multiple interventions (e.g. colloids plus buffered solutions). Therefore we will exclude studies that compare only crystalloids versus colloids, or that compare different types of colloids, even if buffered colloids are used. However, we will include studies with more than two arms if they fulfil all of our inclusion criteria and compare buffered solutions versus isotonic saline.

Types of outcome measures

Primary outcomes

1. Overall (in-hospital) mortality.
2. Acute renal injury during hospitalization as defined by Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage kidney disease (RIFLE), or by Acute Kidney Injury Network (AKIN) criteria.

Secondary outcomes

1. Number of participants with organ system dysfunction (respiratory, haemodynamic, central nervous system and hepatic) as defined in the included studies.
2. Electrolyte disturbances (hyperchloraemic acidosis, serum sodium, potassium, calcium and chloride concentrations, pH, serum bicarbonate, base excess, strong ion difference) measured as serum levels or defined by study authors (e.g. presence or absence of hyperchloraemic acidosis).
3. Blood loss or transfusion requirement.
4. Coagulation disturbances (expressed as thrombocytopenia or coagulopathy).
5. Total volumes of intravenous fluids needed during resuscitation.
6. Quality of life measured with Short Form (SF)-36 and the EuroQOL quality of life questionnaire (EQ-5D) ([Angus 2003](#)).

Search methods for identification of studies

Electronic searches

We will search the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL; current issue); MEDLINE

(access via Ovid, 1946 to date); and EMBASE (access via Ovid SP, 1974 to date).

We will use the search strategy detailed in [Appendix 2](#) and developed by the Cochrane Anaesthesia, Critical and Emergency Care Group Trial Search Co-ordinator. We will adapt the terms used in MEDLINE for searches of the other databases. We will apply no language restrictions and will translate relevant studies if needed.

Searching other resources

We will look for unpublished clinical trials by searching the following websites.

1. Clinicaltrials.gov (www.clinicaltrials.gov).
2. International Standard Randomised Controlled Trial Number Register (<http://www.isrctn.com/>).
3. International Clinical Trials Registry Platform (www.who.int/trialsearch/).
4. Clinical Trial Results (www.clinicaltrialresults.org/).

We will search abstracts from the most relevant meetings from 2000 to date.

1. Society of Critical Care Medicine (SCCM).
2. European Society of Intensive Care Medicine (ESICM).
3. Spanish Society of Intensive Care Medicine (SEMICYUC).
4. American Society of Critical Care Medicine (ASCCM).
5. European Society of Anaesthesiologists (ESA).
6. American Society of Anesthesiologists (ASA).
7. International Anesthesia Research Society (IARS).
8. Spanish Society of Anaesthesia (SEDAR).
9. American Thoracic Society (ATS).
10. American College of Surgeons (ACS).
11. Society of Thoracic Surgeons (STS).

We will contact experts in the field and authors of included studies to ask whether they know of any new eligible studies. We will check the reference lists of all included studies and relevant systematic reviews.

Data collection and analysis

Selection of studies

We will select studies according to the methods of the Cochrane Anaesthesia, Critical and Emergency Care Group. At least two review authors (JAB and AMA) will independently screen all relevant abstracts and titles to determine whether they fulfil the inclusion criteria. We will pilot eligibility criteria on a sample of reports (including studies that the review authors deem definitely eligible, definitely not eligible and doubtful) to ensure their definition. We will classify studies into three categories: 'exclude', 'uncertain' and 'include'; according to pre-determined criteria for this review (see [Criteria for considering studies for this review](#)). At this stage, we will exclude only papers classified as 'exclude'. In the second stage

of the process, the same two review authors will independently examine full-text reports to check whether studies comply with the eligibility criteria of this review. We will resolve disagreements by discussion and will consult a third review author (MC) if we cannot reach consensus. If appropriate, we will contact study authors to clarify the eligibility of a study. Finally, if we cannot obtain necessary information, we will exclude the study in question. We will not be blinded to the names and affiliations of study authors, to journals nor to study results at any stage of the review process.

Data extraction and management

We have modified the Cochrane Anaesthesia, Critical and Emergency Care Group data extraction form (see [Appendix 3](#)) and will pilot this form with five studies to ensure its suitability. Two review authors (JAB and AMA) will independently extract data. We will compare results and will resolve discrepancies by discussion or by consultation with a third review author (MC). We will extract the following information from each trial:

1. Study authors, journal and year of publication.
2. Study design.
3. Study hypothesis.
4. Statistical information: estimation of sample size, statistical power and analysis methods.
5. Participant characteristics: demographics, previous diseases, fulfilment of inclusion criteria, baseline comparability.
6. Intervention and control groups, outcome measures.
7. Results.
8. 'Risk of bias' domains.
9. Conflicts of interest and funding.

One review author (JAB) will enter the data into Review Manager 5 ([RevMan 5.3](#)), and a second review author (AMA) will check data for errors.

Dealing with duplicate publications

If we find several publications that refer to the same trial, we will include the primary version of the study and will reference all secondary reports. We will select the most complete data among all publications found.

Assessment of risk of bias in included studies

Two review authors (JAB and AMA) will independently assess the methodological quality of each trial that fulfils the inclusion requirements of our review. We will extract information related to risk of bias from each study according to the following domains: random sequence generation; allocation concealment; blinding of participants/investigators; outcome assessment; incomplete outcome data; and selective reporting, in accordance with the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). If any of the above data are not available for the publication of interest, or if it is unclear whether

criteria were met, we will contact the study author by email or by letter to request further information. If needed, we will consider other sources of bias related to the design of the studies, as specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). In accordance with recent publications, we will consider industry funding as a potential source of bias (Bero 2013; Lundh 2012). We will consider funding when manpower, materials or grants are provided for the study. We will establish the risk of funding bias as defined in Appendix 4. We will not exclude trials on the basis of risk of bias but will conduct subgroup analyses to explore the effects of risk of bias in the meta-analysis (see Subgroup analysis and investigation of heterogeneity).

Measures of treatment effect

We will perform all analyses according to standards specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). Review authors will select measures of treatment effects according to how data are expressed in studies as follows:

1. Dichotomous data (e.g. need for RRT): risk ratio (RR).
2. Continuous data (e.g. potassium levels): mean difference (MD) and standard deviation (SD), or standardized mean difference (SMD) when original studies use different scales. We will report results with 96.7% confidence intervals (CIs).

Unit of analysis issues

We will deal with trials with cluster or cross-over design as specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Elbourne 2002; Higgins 2011).

Dealing with missing data

We will conduct analyses on an intention-to-treat basis, meaning that:

1. We will analyse participants in the intervention groups to which they were randomized, regardless of the intervention they actually received.
2. We will consider outcome data for all participants and will include all randomized participants in the analysis.

For missing data, we will use this strategy:

1. Contact study authors by email or by letter to request these data.
2. Describe missing outcomes for studies as proportions of participants for whom we have no data with reasons. We will perform sensitivity analyses by using two alternative scenarios for participants with incomplete or missing data for the two primary outcomes considered (overall mortality and acute renal injury during hospitalization) (Jakobsen 2014).

1. 'Best-worst' case scenario analyses: We will consider participants with missing outcome data to be successes in the experimental group and failures in the control group. The denominator includes all participants in the trial.

2. 'Worst-best' case scenario analyses: We will consider participants with missing outcome data to be failures in the experimental group and successes in the control group. The denominator includes all participants in the trial.

Assessment of heterogeneity

We will check for heterogeneity by considering:

1. Clinical and methodological characteristics of studies.
2. Forest plots of study results to visually check for overlaps in confidence intervals.
3. Results of the χ^2 test for statistical heterogeneity (we will consider trial results as heterogeneous when P value < 0.10) and results of the I^2 statistic for quantification of heterogeneity. We will judge the importance of the observed value of I^2 according to the magnitude and direction of effects and the strength of evidence of heterogeneity (from 0% to 40% heterogeneity - may not consider important; from 30 to 60% heterogeneity - may be moderate; from 50% to 90% heterogeneity - may be substantial; and from 75% to 100% heterogeneity - may be considerable) (Deeks 2011). We will explore the reasons behind substantial or considerable heterogeneity by performing subgroup analyses.

Assessment of reporting biases

We will minimize reporting bias by including both published and unpublished studies. We will develop a strategy to search for unpublished studies (Searching other resources) and will look for publication bias in every outcome reported. The pre-defined strategy for assessment of reporting bias will consist of the following:

1. Graphically, if more than 10 studies are included for the considered outcome, we will create a funnel plot (a scatter plot of the intervention effect against a measure of study size).
2. We will assess funnel plot asymmetry statistically if 10 or more studies are meta-analysed.

We will interpret results while considering all causes of asymmetry (not only publication bias).

Data synthesis

We will perform statistical tests according to the recommendations of the Cochrane Anaesthesia, Critical and Emergency Care Group using the Review Manager 5 (RevMan 5.3) package provided by The Cochrane Collaboration for data synthesis and analysis.

Assessment of significance

We will assess our intervention effects by using a random-effects meta-analytical model. If one or two trials dominate 75% of randomized participants, we will use a fixed-effect model (Jakobsen 2014). We will compare results of both models in a sensitivity analysis (see Sensitivity analysis). We consider two co-primary outcomes in our review; therefore, we will consider a P value of 0.03

or less as statistically significant (Jakobsen 2014). We will use the eight-step procedure to assess whether thresholds for significance are crossed (Jakobsen 2014).

Trial sequential analysis

Conventional meta-analyses are at risk of producing random errors as a result of sparse data and repetitive testing of accumulating data (Brok 2008; Brok 2009; Thorlund 2010; Wetterslev 2008; Wetterslev 2009). We will perform trial sequential analyses (TSA) (Thorlund 2011) on outcomes to calculate the optimum information size (e.g. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) (Wetterslev 2008) and the breach of the cumulative Z-curve of relevant trial sequential monitoring boundaries. We will report whether trial sequential monitoring boundaries for benefit, harm or futility are crossed. For dichotomous outcomes, we will estimate the required information size on the basis of the proportion of participants with an outcome in the control group, a relative risk reduction of 20%, an alpha of 3% (Jakobsen 2014), a beta of 20% and the diversity suggested by trials in the meta-analysis. For continuous outcomes, we will estimate the required information size according to the SD observed in the control group of trials with low risk of bias and a minimal relevant difference of 50% of this SD, an alpha of 3%, a beta of 20% and the diversity suggested by trials in the meta-analysis. We will use TSA software for these analyses (Thorlund 2011).

Subgroup analysis and investigation of heterogeneity

If the number of studies is appropriate, we will conduct subgroup analyses to examine the following.

Participant subsets

1. Neurocritical participants.
2. Septic participants.
3. Burn or trauma participants.
4. Surgical critical ill participants.
5. Participants with primary hydroelectrolytical imbalance (dehydration or diabetic ketoacidosis).

Intravenous buffered fluid received

1. Fluids containing bicarbonate as buffer.
2. Fluids containing a bicarbonate precursor as buffer.

Age group

1. Adults $\geq$ 16 years old.
2. Children < 16 years old.

Risk of bias

1. Trials with low risk of bias.
2. Trials with unclear or high risk of bias.

We will assess differences between subgroups by performing the test of interaction (Altman 2003).

Summary of findings

We will design a 'Summary of findings' table using GRADE profiler (GRADEpro 0.4.8) software to summarize the key results of our review. We will indicate in this table the population, intervention and comparison, along with relevant outcomes.

We will use the GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) system (Guyatt 2008) to assess the quality of evidence associated with each outcome: overall (in-hospital) mortality, acute renal failure, organ system dysfunction, electrolyte disturbances, transfusion requirements, coagulation disturbances, total volume of fluids needed. The GRADE approach appraises the quality of evidence according to the extent to which one can be confident that an estimate of effect or association reflects the item assessed. Two review authors (JAB and AMA) will independently assess the quality of the body of evidence for the design of the 'Summary of findings' table. Our confidence in the estimate of effect will be evaluated in terms of study limitations, consistency of effect, imprecision indirectness and publication bias. We will use trial sequential analysis as a supplement for a more thorough assessment of imprecision (Guyatt 2011).

Sensitivity analysis

We will undertake the following sensitivity analyses.

1. Evaluate the impact of risk of bias from individual trials in the magnitude or direction of overall effect. We will exclude studies with high or unclear risk of bias in the following domains: allocation features, levels of missing data and blinding of outcome assessment.
2. Explore potential differences when the fixed-effect model versus the random-effects model is used.

ACKNOWLEDGEMENTS

The review authors would like to thank Jane Cracknell, Managing Editor, Cochrane Anaesthesia, Critical and Emergency Care Group (ACE), for help with organization of the review, and Karen Hovhannisyan, former Trials Search Co-ordinator, for help with identification of search terms.

We would like to thank Harald Herkner (Content Editor); Cathal Walsh (Statistical Editor); and Edward Burdett and Jørn Wetterslev (Peer Reviewers) for help and editorial advice provided during

preparation of this protocol for the systematic review. The contributions of the Cochrane Collaborating Centre in Madrid are gratefully acknowledged.

We also would like to thank the Intensive Care Department of the 12 de Octubre Hospital (Madrid), with special thanks to the Head of the Department, Juan Carlos Montejo.

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* Indicates the major publication for the study

APPENDICES

Appendix I. Types of fluids/solutions

	Plasma	Isotonic saline	Buffered solutions (relative low-chloride solutions)			
			Hartmann's	Ringer's lactate	Ringer's acetate	Plasma-Lyte 148
Osmolarity (mOsm/L)	280-296	308	278	273	275	294
pH	7.4	4.5-7	5-7	5.5-7	6.7	6.5-8
Sodium (mmol/L)	140	154	131	130	131	140
Potassium (mmol/L)	5	-	5.4	4	4	5
Calcium (mmol/L)	2.2	-	1.8	1.5	1	-
Magnesium (mmol/L)	1	-	-	-	-	1.5
Chloride (mmol/L)	100	154	112	111	109	98
Buffers (mmol/L)	Bicarbonate (24) Lactate (1)	-	Lactate (29)	Lactate (28)	Acetate (28)	Gluconate (23) Acetate (27)

1 exp Isotonic Solutions/ or Fluid Therapy/ or Hydroxyethyl Starch Derivatives/ or Electrolytes/ or Sodium Chloride/ or Plasma Substitutes/ or crystalloid*.ti,ab. or (hydroxyethyl starch or HES).mp. or (saline adj4 (isotonic or normal or plasma?lyte)).mp. or ((fluid* adj3 (therap* or resuscitat* or administrat* or intraven* or IV or solution* or composition or regimen* or management or *buffer*/ or (chloride adj3 (liberal or restrictive))))).ti,ab. or solution* adj4 (buffer* or non?buffer* or isotonic or sodium chloride or NaCl or bocarbonat* or lactated ringer* or electrolyte or balanced or ringer or hartmann or acetated or(chlorid* adj2 rich) or infused)).ti,ab. or (bocarbonat* adj3 (buffer* or precursor*)).mp.

2 exp Resuscitation/ or exp Intensive Care/ or exp Critical Care/ or exp Critical Illness/ or resuscitat*.ti,ab. or ((department* or care*) adj4 (critical* or intensive or emergency)).ti,ab. or (critical* adj3 ill*).ti,ab. or (shock adj3 syndrom*).ti,ab. or ((burn* or trauma*) adj3 severe).ti,ab. or (pancreatitis or septic or sepsis or intoxicat* or dehydrat*).ti,ab. or injuri*.ti,ab. or (hemorrhagic adj3 shock).ti,ab. or (diabetic adj3 ketoacidosis).ti,ab. or (hyperchloremic adj3 acidosis).ti,ab.

3 1 and 2

4 ((randomised controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.

5 3 and 4

Review title or ID
Study ID <i>(surname of first author and year first full report of study was published, e.g. Smith 2001)</i>
Report IDs of other reports of this study <i>(e.g. duplicate publications, follow-up studies)</i>
Notes:

Buffered solutions versus isotonic saline for resuscitation in non-surgical critically ill adults and children (Protocol) 11

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3.2 Study eligibility

Study characteristics	Eligibility criteria <i>(insert eligibility criteria for each characteristic as defined in the protocol)</i>	Yes	No
Type of study	Randomized controlled trial		
	Controlled clinical trial		
Participants			
Types of interventions			
Types of outcome measures			
INCLUDE		EXCLUDE	
Reason for exclusion			
Notes:			

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

3.3 Population and setting

	Description <i>Include comparative information for each group (i.e. intervention and control), if available</i>	Location in text <i>(pg & 1/fig/table)</i>
Population description <i>(from which study participants are drawn)</i>		
Setting <i>(including location and social context)</i>		
Inclusion criteria		
Exclusion criteria		
Method/s of recruitment of participants		

(Continued)

Informed consent obtained	Yes/No/Unclear	
Notes:		

3.4 Methods

	Descriptions as stated in report/paper	Location in text (pg & #fig/table)
Aim of study		
Design (e.g. parallel, cross-over, cluster)		
Unit of allocation (by individuals, cluster/groups or body parts)		
Start date		
End date		
Total study duration		
Funding (if present indicate)	Yes/No	
Conflict of interest	Report: Yes/No Present: Yes/No	
Ethical approval needed/obtained for study	Yes/No/Unclear	
Notes:		

3.5 Risk of bias assessment

Domain	Risk of bias			Support for judgement	Location in text (pg & §/fig/table)
	Low	High	Unclear		
Random sequence generation (selection bias)					
Allocation concealment (selection bias)					
Blinding of participants and personnel (performance bias)				Outcome group: All/	
(if required)				Outcome group:	
Blinding of outcome assessment				Outcome group: All/	
(if required)				Outcome group:	
Incomplete outcome data (attrition bias)					
Selective outcome reporting? (reporting bias)					
Funding (Appendix 4)					
Other bias					
Notes:					

3.6 Participants

Provide overall data and, if available, comparative data for each intervention and comparison group.

	Descriptions as stated in report/paper	Location in text (pg & I/fig/table)
Total no. randomized (or total pop. at start of study for NRCTs)		
Clusters (if applicable, no., type, no. people per cluster)		
Baseline imbalances		
Withdrawals and exclusions (if not provided below by outcome)		
Age		
Sex		
Race/Ethnicity		
Severity of illness		
Co-morbidities		
Other treatment received (additional to study intervention)		
Other relevant sociodemographics		
Subgroups measured		
Subgroups reported		
Notes:		

3.7 Intervention groups

Copy and paste table for each intervention and comparison group.

Intervention group 1

	Descriptions as stated in report/paper	Location in text (pg & I/fig/table)
Group name		
No. randomized to group (specify whether no. people or clusters)		
Theoretical basis (include key references)		
Description (include sufficient detail for replication, e.g. content, dose, components)		
Duration of treatment period		
Timing (e.g. frequency, duration of each episode)		
Delivery (e.g. mechanism, medium, intensity, fidelity)		
Providers (e.g. no., profession, training, ethnicity, etc., if relevant)		
Co-interventions		
Economic variables (i.e. intervention cost, changes in other costs as result of intervention)		
Resource requirements to replicate intervention (e.g. staff numbers, cold chain, equipment)		
Notes:		

3.8 Outcomes

Copy and paste table for each outcome.

Outcome 1

	Descriptions as stated in report/paper	Location in text (pg & ffig/table)
Outcome name		
Time points measured		
Time points reported		
Outcome definition (with diagnostic criteria if relevant)		
Person measuring/reporting		
Scales: upper and lower limits (indicate whether high or low score is good)		
Is outcome/tool validated?	Yes/No/Unclear	
Imputation of missing data (e.g. assumptions made for ITT analysis)		
Assumed risk estimate (e.g. baseline or population risk noted in Background)		
Power		
Notes:		

3.9 Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

Dichotomous outcome

	Descriptions as stated in report/paper				Location in text <i>(pg & #fig/table)</i>
Comparison					
Outcome					
Subgroup					
Time point <i>(specify whether from start or end of intervention)</i>					
Results	Intervention		Comparison		
	No. events	No. participants	No. events	No. participants	
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					
Statistical methods and appropriateness of these methods <i>(e.g. adjustment for correlation)</i>					
Reanalysis required? <i>(specify)</i>	Yes/No/Unclear				
Reanalysis possible?	Yes/No/Unclear				
Reanalysed results					

(Continued)

Notes:

Continuous outcome

	Descriptions as stated in report/paper						Location in text (pg & ¶/fig/table)
Comparison							
Outcome							
Subgroup							
Time point (specify whether from start or end of intervention)							
Results	Intervention			Comparison			
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants	
No. missing participants and reasons							
No. participants moved from other group and reasons							
Any other results reported							
Statistical methods and appro-							

(Continued)

priateness of these methods (e.g. adjustment for correlation)		
Reanalysis required? (specify)	Yes/No/ Unclear	
Reanalysis possible?	Yes/No/ Unclear	
Reanalysed results		
Notes:		

Other outcome

	Descriptions as stated in report/paper				Location in text (pg & ¶/fig/table)
Comparison					
Outcome					
Subgroup					
Time point (specify whether from start or end of intervention)					
Results	Intervention result	SD (or other variance)	Control result	SD (or other variance)	
	Overall results		SE (or other variance)		
No. participants	Intervention		Control		

(Continued)

No. missing participants and reasons			
No. participants moved from other group and reasons			
Any other results reported			
Statistical methods and appropriateness of these methods (<i>e.g. adjustment for correlation</i>)			
Reanalysis required? (<i>specify</i>)	Yes/No/ Unclear		
Reanalysis possible?	Yes/No/ Unclear		
Reanalysed results			
Notes:			

3.10 Applicability

Have important populations been excluded from the study? <i>(consider disadvantaged populations, possible differences in the intervention effect)</i>	Yes/No/Unclear
Is the intervention likely to be aimed at disadvantaged groups? <i>(e.g. lower socioeconomic groups)</i>	Yes/No/Unclear
Does the study directly address the review question? <i>(any issues of partial or indirect applicability)</i>	Yes/No/Unclear
Notes:	

3.11 Other information

	Descriptions as stated in report/paper	Location in text <i>(pg & ¶/fig/table)</i>
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information <i>(from whom, what and when)</i>		
Notes:		

Appendix 4. Criteria for other bias (funding source)

Funding	
Criteria for a judgement of 'low risk' of bias	<ul style="list-style-type: none"> - Study authors report non-profit sources of funding (hospital or governmental funding) - Non-funded trials
Criteria for a judgement of 'high risk' of bias	<ul style="list-style-type: none"> - Study authors report profit sources of funding - Study authors report mixed sources (profit and non-profit) - Sponsor involved in analysis or design
Criteria for a judgement of 'unclear risk' of bias	<ul style="list-style-type: none"> - Funding not reported or sponsor's role not clearly specified

WHAT'S NEW

Date	Event	Description
3 January 2019	Amended	Editorial team changed to Cochrane Emergency and Critical Care

CONTRIBUTIONS OF AUTHORS

Jesús A Barea-Mendoza (JAB), Alba M Antequera (AMA), Maria N Plana (MNP), Mario Chico-Fernández (MC), Alfonso Muriel (AM), Ignacio Sáez (IS), José M Estrada-Lorenzo (JME).

Conceiving of the review: JAB.

Designing the review: JAB.

Co-ordinating the review: JAB, MNP.

Collecting data for the review: JAB, AMA.

Designing search strategies: JME, JAB, AMA.

Screening search results: JAB, AMA, JME.

Organizing retrieval of papers: JAB, AMA, JME, IS.

Screening retrieved papers against eligibility criteria: JAB, AMA, IS, MC.

Appraising the quality of papers: AMA, JAB, IS, MC.

Extracting data from papers: JAB, AMA, IS.

Writing to authors of papers for additional information: AMA, IS.

Providing additional data about papers: JME, AMA, IS.

Obtaining and screening data from unpublished studies: JME, AMA, IS.

Managing data for the review: JAB, AMA.

Entering data into RevMan: JAB.

Analysing data: MNP, AM, JAB.

Interpreting data: JAB, AMA, MNP, AM, MC, IS.

Providing a methodological perspective: MNP, AM.

Providing a clinical perspective: JAB, AMA, IS, MC.

Providing a policy perspective: MC, JAB.

Writing the review (or protocol): JAB, AMA, MNP, AM, IS, MC.

Providing general advice on the review: JAB.

Securing funding for the review: MC.

Performing previous work that was the foundation of the current review: JAB.

DECLARATIONS OF INTEREST

Jesús A Barea-Mendoza has no conflicts of interest to declare.

Alba M Antequera has no conflicts of interest to declare.

Maria N Plana has no conflicts of interest to declare.

Mario Chico-Fernández has no conflicts of interest to declare.

Alfonso Muriel has no conflicts of interest to declare.

Ignacio Sáez has no conflicts of interest to declare.

Jose M Estrada-Lorenzo has no conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- No sources of support supplied