



# Are Balanced Crystalloid Solutions Better Than Normal Saline Solution for the Resuscitation of Children and Adult Patients?

## TAKE-HOME MESSAGE

Compared with 0.9% normal saline solution, balanced crystalloid solutions are not associated with differences in mortality, acute kidney injury, or organ-system dysfunction among critically ill patients. It is reasonable to use either fluid in patients undergoing resuscitation with small volumes (1 to 2 L) in the emergency department (ED).

## METHODS

### DATA SOURCES

The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and the Cumulative Index of Nursing and Allied Health were searched from inception to July 2018 with a combination of key words and Medical Subject Headings terms, without language or publication restrictions. Four trial registries were also searched to identify studies in progress. Additionally, abstracts from anesthesiology, critical care, and surgical societies were screened from 2000 to 2018. The investigators reviewed the bibliographies of included articles and contacted the authors for additional relevant references.

### STUDY SELECTION

The review included all randomized controlled trials comparing balanced crystalloid solutions versus intravenous 0.9% saline solution among adult and pediatric patients in a critical care setting.<sup>1</sup> Only parallel- or crossover-design studies were included. Studies with patients undergoing elective

### EBEM Commentators

Michael Gottlieb, MD  
Vanessa Petrak, MD  
Christine Binkley, MD, MPH  
*Department of Emergency Medicine  
Rush University Medical Center  
Chicago, IL*

*Jestin N. Carlson, MD, MS, and Alan Jones, MD, serve as editors of the SRS series.*

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **Antequera Martín AM, Barea Mendoza JA, Muriel A, et al. Buffered solutions versus 0.9% saline solution for resuscitation in critically ill adults and children. *Cochrane Database Syst Rev.* 2019;(7):CD012247.**

## Results

Comparison of balanced crystalloid solutions with normal saline solution.

Outcome	No. of Studies		
	(No. of Participants)	OR (95% CI)	Heterogeneity ( $I^2$ ), %
Inhospital mortality	14 (19,664)	0.91 (0.83–1.01)	0
Acute kidney injury	9 (18,701)	0.92 (0.84–1.00)	0
Organ-system dysfunction	5 (266)	0.80 (0.40–1.61)	0

OR, Odds ratio; CI, confidence interval.

The authors identified 10,286 records, with 21 studies (n=20,213 participants) selected for inclusion. Studies were published between 1999 and 2018. The studies were conducted with both critically ill children and adults, including those with sepsis, trauma, burns, or shock. Only 4 studies included children and none of them assessed kidney damage.

Balanced solutions were not associated with an effect on in-hospital mortality, acute kidney injury, or organ-system dysfunction (Table). For electrolyte disturbances, subgroups of sodium, potassium, chloride, pH, and bicarbonate were examined. No difference was found between the 2 groups for sodium or potassium. Compared with the 0.9% saline solution

surgery and studies with multiple interventions in the same arm were excluded. The primary outcomes were rates of overall in-hospital mortality and acute kidney injury during hospitalization. Secondary outcomes included the presence of organ-system dysfunction, electrolyte disturbances during admission, transfusion requirements, total volume of intravenous fluids needed during resuscitation, and cost. Subgroup analyses were performed by participants subsets, type of balanced crystalloid solution, age group, and risk of bias. Initial study selection was screened by at least 2 independent reviewers. All articles passing initial screening underwent full-text review by the same 2 authors. Disagreements were resolved by discussion with a third review author, and studies were excluded if the necessary information to determine eligibility was not obtainable.

### DATA EXTRACTION AND SYNTHESIS

Two investigators extracted the data with a predesigned form. Risk of bias was assessed with the Cochrane Risk of Bias Tool.<sup>2</sup> Odds ratios were calculated for dichotomous data. Continuous data were presented as mean difference or standardized mean difference (when different scales were used) with SDs. Outcomes were reported with 95% confidence intervals. Heterogeneity was assessed with the  $\chi^2$  and  $I^2$  statistics. Publication bias was assessed with a funnel plot.

group, the balanced solution group had a higher pH, higher bicarbonate level, and lower chloride level. There was no evidence of publication bias.

### Commentary

Intravenous fluids are one of the most common interventions among critically ill patients, with more than one third of all hospitalized patients receiving them.<sup>3</sup> In fact, it has been estimated that greater than 200 million liters of intravenous fluids are used in the United States each year.<sup>4</sup> Although 0.9% normal saline solution is a widely used crystalloid solution, it can lead to a hyperchloremic metabolic acidosis, which has been associated with complications in some studies.<sup>5,6</sup> The ideal fluid choice should keep electrolytes and pH near physiologic levels while expanding intravascular volume.<sup>7</sup> However, these “balanced” solutions are not universally available and can be significantly more costly than 0.9% normal saline solution.<sup>8</sup> Therefore, it is important to determine whether there is a clinically significant benefit associated with these more balanced crystalloid solutions.

Overall, this meta-analysis found no statistically significant difference in the rate of in-hospital mortality, acute kidney injury, or organ-system dysfunction between 0.9% normal saline solution and balanced crystalloid solutions. However, it is important to consider several limitations with respect to this review. First, there was significant clinical heterogeneity between the studies. Patients were enrolled in different settings and at different times during their critical illness. Although the authors did limit their search to the critical care setting, the specific definition of a critical care setting (eg, ED, ICU, operating room) was

not defined, which may have further added to the potential heterogeneity. Additionally, there was variability in regard to the volume and timing of fluids between studies, as well as whether patients received any fluids before enrollment. Patients were included with a wide variety of disease states and it is unclear whether certain disease states may benefit from a specific type of solution. Moreover, several different types of balanced crystalloid solutions with different concentrations of electrolytes were used in the included trials. Specific outcome definitions also varied between studies. For example, acute kidney injury can be defined by multiple criteria and encompasses a broad spectrum of severity. Transient elevations in creatinine level are of less significance than the requirement for renal replacement therapy, with the latter being more clinically relevant to patients. All outcomes were based on low-certainty or very-low-certainty evidence except for mortality.

Total fluid volume was incompletely reported in several of the studies. Additionally, most studies had relatively small sample sizes, with the majority of patients being from 2 studies.<sup>9,10</sup> In those 2 studies, the mean fluid volume administered to both groups was approximately 1 L. It is unclear whether these data would apply to patients receiving larger fluid volumes. Pediatric patients composed a small portion of the total sample and tended to be less sick than their adult counterparts. Moreover, 2 of the pediatric studies evaluated patients with dengue shock syndrome, which may not be easily translated to

other patient populations. There were also very limited data on neurocritically ill patients; they were excluded from many studies because balanced solutions have a lower osmolarity than 0.9% normal saline solution. Two studies received funding through unrestricted pharmaceutical grants, 1 received pharmaceutical funding without explicit statement of the company's role, and 5 did not report whether funding was received. The influence of this on the findings is unclear and is another limitation of the study. Finally, many studies did not blind to the type of solution.

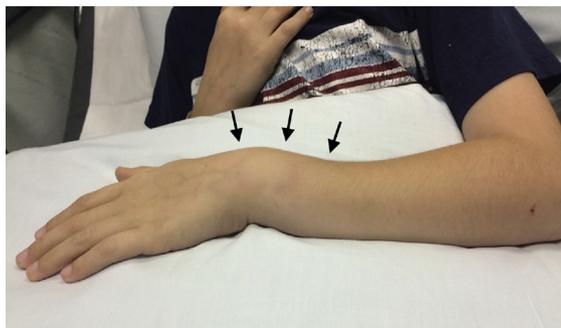
Future studies should assess this among pediatric patients, among those with neurocritical illnesses,

and by using standardized outcome measures.

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“Child With Dinner Fork Deformity” by Kardouni, February 2016, Volume 67, #2, pp. 165, 188.