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Saline-Induced Hyperchloremic Metabolic Acidosis: A Systematic Review

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KEYWORDS
Hyperchloremic metabolic acidosis; saline solutions; balanced crystalloids; normal saline; hypertonic saline; metabolic stability; Systematic review.

ABSTRACT:

Objectives: To systematically review and synthesize available literature on saline-induced hyperchloremic metabolic acidosis (HMA).

Methods: A comprehensive search across four databases identified 209 publications. Duplicates were removed using Rayyan QCRI, and relevance screening reduced the selection to 40 full-text articles. After further review, seven studies met the inclusion criteria.

Results: We included seven studies with a total of 205 participants who received saline infusion and the majority 129 (62.9%) were males. The incidence of HMA following saline infusion ranged from 54.8% in pediatric septic shock cases to 100% in healthy volunteers receiving hypertonic saline. Saline solutions, particularly normal and hypertonic saline, are frequently associated with metabolic disturbances, including HMA and reduced acid-base balance, especially in surgical and critically ill patients. In contrast, balanced crystalloid solutions do not induce HMA and support better patient outcomes by maintaining metabolic stability. Balanced salts significantly reduce the incidence of HMA in pediatric septic shock and enhance tissue perfusion while reducing acidosis risk in elderly surgical patients.

Conclusion: This review highlights the metabolic risks of saline solutions and the clear benefits of balanced crystalloids in preventing HMA. Transitioning to balanced fluids in clinical practice can enhance patient safety and outcomes across various settings. Further research is needed to explore long-term impacts and develop standardized guidelines for intravenous fluid use, ensuring evidence-based care and minimizing complications.

Introduction

HMA acidosis is a clinical condition that combines non-respiratory acidosis, or metabolic acidosis brought on by an increase in chloride plasma concentration to values above physiological limits [1].

At this time, the pathogenesis of HMA can be explained in two ways. Dr. Stewart's physicochemical approach is the first; the second is only a dilutional explanation for a decrease in plasma bicarbonate upon intravenous infusion of non-bicarbonate-containing fluids. However, recent research indicates that the dilutional explanation might not be as plausible [2].

The most frequent preventable cause of HMA is most likely the administration of fluids with adequate supraphysiological chloride concentrations, like 0.9% saline. 154 mmol of sodium chloride is supraphysiological (normal range 98-107 mmol/L) and contains 154 mmol of sodium, which is consistent with that found in the extracellular space. As previously explained, the resulting acidosis is mostly caused by a drop in the plasma's strong ion difference [1].

Animal models have clearly shown hyperchloremic acidosis after saline treatment. As shown below, there is now solid proof that it occurs in humans [3]. Though perspectives continue to vary, there has been substantial discussion over the supposedly benign character of HMA. Although it appears improbable given that the pH drop is frequently moderate and out of proportion to the symptoms and indications, it is uncertain if the pH drop itself is to blame for the related clinical symptoms. It could be the consequence of interference with red cell structure and function or a chemical reaction brought on by supraphysiological levels of chloride. Some of these questions may be addressed by the evidence listed below, but not all of them [4, 5].

This review aims to systematically review and synthesize available literature on saline-induced HMA, focusing on its pathophysiology, clinical implications, diagnostic approaches, and management strategies, with the aim of informing clinical decision-making and identifying areas requiring further investigation.

Methods

Search strategy

The PRISMA and GATHER criteria were followed for the systematic review. An overall search was conducted to identify relevant studies related to the available literature on saline-induced HMA. The following four electronic databases were used by the reviewers for searching: SCOPUS, Web of Science, Cochrane, and PubMed. We removed any duplicates and uploaded all the titles and abstracts we could find through electronic searches onto Rayyan. After that, all the study texts that met the inclusion criteria based on the abstract or title were collected for a full-text examination. Two reviewers independently evaluated the extracted papers' suitability and discussed any discrepancies.

Study population—selection

The PICO (Population, Intervention, Comparator, and Outcome) factors were implemented as inclusion criteria for our review: (i) Population: Patients receiving saline infusions (e.g., surgical patients, critically ill patients, or those requiring fluid resuscitation), (ii) Intervention: Administration of normal saline (0.9% NaCl) as the primary intravenous fluid or hypertonic saline, (iii) Comparator: Administration of alternative intravenous fluids (e.g., balanced crystalloids like Lactated Ringer’s or Plasma-Lyte), (iv) Outcomes: Incidence or severity of HMA, as measured by chloride levels, base deficit, pH levels, and/or clinical outcomes.

Data extraction

Data from studies that satisfied the inclusion requirements were extracted by two objective reviewers using a predetermined and uniform methodology. The following information was retrieved and recorded: (i) First author (ii) Year of publication, (iii) Study design, (iv) Country, (v) Sample size, (vi) Age, (vii) Gender, (viii) Population type, (ix) Saline type, (x) Incidence of HMA (%), (xi) Main outcomes.

Quality review

The Cochrane Risk of Bias Instrument [6] was used to conduct a critical appraisal of the identified RCTs. This tool evaluates the risk of bias in seven fields: arbitrary sequence generation, allocation secrecy, blinding of participants and employees, blinding of outcome evaluation, inadequate outcome data, selective reporting, and additional bias sources. The risk of bias in each of these domains was classified as low, unclear, or high.

Results

The specified search strategy yielded 209 publications **(Figure 1).** After removing duplicates (n = 98), 111 trials were evaluated based on title and abstract. Of these, 71 failed to satisfy eligibility criteria, leaving just 40 full-text articles for comprehensive review. A total of 7 satisfied the requirements for eligibility with evidence synthesis for analysis.

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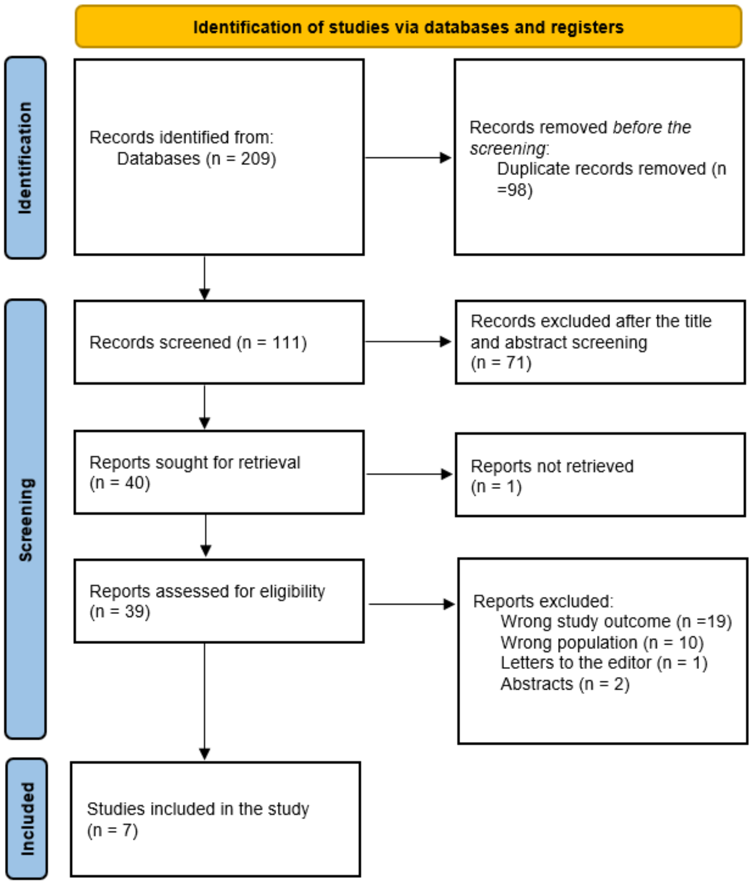

Figure (1): PRISMA flowchart [7].

Sociodemographic and clinical outcomes

We included seven studies with a total of 205 participants who received saline infusion and the majority 129 (62.9%) were males. Regarding study designs, all of the included studies were RCTs [8-14]. Four studies were implemented in India [9-12], one in Sweden [8], one in Thailand [13], and one in the UK [14]. The earliest study was conducted in 2001 [14] and the latest in 2023 [10].

The incidence of HMA following saline infusion ranged from 17 (54.8%) in pediatric septic shock received normal saline [13] 100% in healthy volunteers received hypertonic saline [8]. The main outcomes of the studies demonstrate that HMA is a frequent complication associated with the use of saline solutions, particularly normal and hypertonic saline. It was pointed out that normal saline is often associated with metabolic disturbances, such as hyperchloremic acidosis and reduced acid-base balance, especially in surgical and critically ill patients [8], [9], [10].

On the other hand, it has been observed that the infusion of balanced crystalloid solutions does not lead to the development of HMA. Clinical use of such solutions seems to support better patient outcomes by preserving their metabolic stability. This is particularly true for specific groups, such as neurosurgical [9], [10], [11], and gastrointestinal surgery patients, in whom the substitution of normal saline with balanced solutions improved metabolic and clinical outcomes [12].

The studies also indicated that, in pediatric patients with septic shock, balanced salts are superior to the usual saline in that they reduce significantly the incidence of HMA [13]. In elderly surgical patients, there was also the use of intraoperative balanced crystalloid or colloid solutions that enhanced tissue perfusion and reduced the risk of acidosis when compared to saline-based solutions [14].

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Table (1): Outcome measures of the included studies

Study ID	Study design	Country	Sociodemographic	Population type	Saline type	HMA (%)	Main outcomes
Moen et al., 2014 [8]	RCT	Sweden	N= 19 Mean age: 28 Males: 10 (52.9%)	Healthy volunteers	Hypertonic saline	19 (100%)	All participants experienced HMA and a reduction in strong ion difference after receiving an infusion of hypertonic saline.
Dey et al., 2018 [9]	RCT	India	N= 22 Mean age: 45.9 Males: 11 (50%)	Neurosurgical patients	Normal saline	NM	Selecting a balanced crystalloid electrolyte solution can help avoid HMA and other issues that arise from regular saline infusion.
Shrivastava et al., 2023 [10]	RCT	India	N= 40 Mean age: 39.1 Males: 28 (70%)	Neurosurgical patients	Normal saline	NM	Using balanced crystalloids can help prevent HMA, which can be caused by normal saline. For neurosurgical patients, balanced crystalloids should be used instead of regular saline in order to improve metabolic

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							status and clinical results.
Bhagat et al., 2019 [11]	RCT	India	N= 28 Mean age: 38 Males: 19 (67.5%)	Neurosurgical patients	Normal saline	NM	Ionic hypocalcemia and HMA were linked to the usage of regular saline.
Brahma et al., 2019 [12]	RCT	India	N= 41 Mean age: 44.4 Males: 27 (65.8%)	Patients undergoing GIT surgeries	Normal saline	33 (80.48%)	Unlike regular saline-based crystalloid treatments, the administration of a balanced solution prevents the development of HMA.
Anantasit et al., 2020 [13]	RCT	Thailand	N= 31 Mean age: 5.35 Males: 22 (70.9%)	Pediatric septic shock	Normal saline	17 (54.8%)	while compared to balanced salt, children with septic shock tended to have HMA more frequently while using regular saline solution.
Wilkes et al., 2001 [14]	RCT	UK	N= 24 Mean age: 73.1 Males: 12 (50%)	Elderly surgical patients	Normal saline	16 (66.7%)	When compared to saline-based solutions, the administration of balanced crystalloid and colloid solutions in older postoperative patients enhanced gastric

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							mucosal perfusion and avoided the development of HMA.

Figure (2): Risk of bias assessment.

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Discussion

To our knowledge, this review is the first comprehensive review discussing the relation of saline infusions to the development of HMA. These findings point clearly to saline solutions and more precisely to normal saline as effective solutions able to create a number of serious metabolic disorders among diverse groups of patients. The reviewed studies indicate that the common result consistently reported from the use of saline, especially in surgical, critically ill, and pediatric patients, is HMA. On the other hand, balanced crystalloid solutions have been shown to prevent such changes, and thus there is a need for revision of the current concepts on fluid resuscitation and intravenous therapy.

Eisenhut found that hyperchloraemic acidosis's safety has not been proven in prospective studies or in individuals with various serious illnesses. A slow replacement approach is safer than quick infusions, and more physiological electrolyte solutions (such Ringer's lactate solution) may be better than isotonic saline, especially in critically sick patients with co-morbidities like renal illness [15]. Acidosis results from both excessive renal bicarbonate removal and a reduction in the strong anion gap caused by an excessive increase in plasma chloride. Hartmann's solution with 6% hetastarch and a balanced electrolyte and glucose solution were compared to isotonic saline infusion in a randomized controlled trial with a mixed sample of patients undergoing major surgery. HMA occurred in two-thirds of patients in the isotonic saline group but not in any of the patients in the balanced fluid group [14]. Decreased gastric mucosal permeability on gastric tonometry was linked to hyperchloremic acidosis. This finding was supported by another randomized double-blind study comparing lactated Ringer's to isotonic saline in patients having aortic reconstructive surgery. The acidosis necessitated treatments such as bicarbonate infusion and was linked to the use of additional blood products [16].

The review also puts into perspective the variability in incidence and severity of HMA, relating to clinical context, population characteristics, and type of saline used. This variability again brings to the fore the need for individualization of intravenous fluid therapy to meet the needs of the patient, thus minimizing adverse effects and optimizing clinical outcomes. **Skellett *et al.*** reported that correcting the anomaly may be the primary negative consequence of saline-induced hyperchloremic acidosis. Acidosis is frequently interpreted as a sign of inadequate myocardial function or organ perfusion, and a negative base excess may lead to the use of blood products, increased inotrope support, the application of boluses of more saline-containing fluids, and the start of ventilatory support [17].

These findings are of great clinical significance, with a reconsideration of the routine use of normal saline during fluid management. Shifting to the use of balanced crystalloid solutions may ensure a lower rate of HMA, better metabolic stability, and possibly improved overall patient outcomes. This may be particularly significant in neurosurgical, gastrointestinal surgery, pediatric, and elderly patient populations, based on emerging literature that suggests higher complication rates associated with saline infusions among these groups.

Strengths

One of the strengths of this review is that it focuses on a topic that has not been fully reviewed in the past. It also includes studies with varied patient populations and different clinical settings, which increases the generalizability of findings. Furthermore, the review presents a consistent pattern across studies that reinforces the reliability of the conclusion. The insights provided offer a practical framework through which healthcare providers could improve intravenous fluid management and reduce complications.

Limitations

Still, the review has some limitations. The studies included in this review have small sample sizes, different populations, and different study designs, which can affect the consistency of the results. Most studies target specific populations, such as surgical or critically ill patients; thus, generalizing their findings to other groups may pose difficulties. Also, most of the studies had a lack of long-term follow-up data, which allows further limitation on the assessment of long-term effects of saline-induced HMA.

Conclusion

This review underlines the major metabolic risks of saline solutions and indicates the obvious advantages of the use of balanced crystalloid solutions to avoid HMA.

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It would thus appear that a transition to balanced fluids in daily practice may not only improve safety for patients but also overall outcomes in a multitude of settings. Further research is needed to address the long-term implications of saline-induced metabolic acidosis and to establish standard guidelines on best practice for intravenous fluid use. Evidence-based practice will ensure better care and reduce avoidable complications.

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