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0.9% NaCl (Normal Saline)—Perhaps not so normal after all?

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Abstract

Crystalloid infusion is widely employed in patient care for volume replacement and resuscitation. In the United States the crystalloid of choice is often normal saline. Surgeons and anesthesiologists have long preferred buffered solutions such as Ringer's Lactate and Plasma-Lyte A. Normal saline is the solution most widely employed in medical and pediatric care, as well as in hematology and transfusion medicine. However, there is growing concern that normal saline is more toxic than balanced, buffered crystalloids such as Plasma-Lyte and Lactated Ringer's. Normal saline is the only solution recommended for red cell washing, administration and salvage in the USA, but Plasma-Lyte A is also FDA approved for these purposes. Lactated Ringer's has been traditionally avoided in these applications due to concerns over clotting, but existing research suggests this is not likely a problem. In animal models and clinical studies in various settings, normal saline can cause metabolic acidosis, vascular and renal function changes, as well as abdominal pain in comparison with balanced crystalloids. The one extant randomized trial

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suggests that in very small volumes (2 liters or less) normal saline is not more toxic than other crystalloids. Recent evidence suggests that normal saline causes substantially more *in vitro* hemolysis than Plasma-Lyte A and similar solutions during short term storage (24 hours) after washing or intraoperative salvage. There are now abundant data to raise concerns as to whether normal saline is the safest replacement solution in infusion therapy, red cell washing and salvage, apheresis and similar uses. In the USA, Plasma-Lyte A is also FDA approved for use with blood components and is likely a safer solution for these purposes. Its only disadvantage is a higher cost. Additional studies of the safety of normal saline for virtually all current clinical uses are needed. It seems likely that normal saline will eventually be abandoned in favor of safer, more physiologic crystalloid solutions in the coming years.

Keywords

resuscitation; hemolysis; crystalloid; saline; transfusion

INTRODUCTION

The use of crystalloid for both volume replacement and resuscitation is ubiquitous in medical practice. The choice of crystalloid is, however, quite variable, and without clear evidence base. In the USA and Europe, 0.9% NaCl, referred to as “normal saline” is the most widely used crystalloid, particularly in medical and pediatric practice,[1] but many surgeons, anesthesiologists and intensivists prefer “balanced solutions” with buffering capacity such as Ringer’s Lactate or Plasma-Lyte A.[2, 3] In transfusion medicine, normal saline is uniformly employed, and is the only solution recommended by the AABB as compatible with blood components. Normal saline is invariably the solution utilized for initial intravenous infusions and washing/salvaging red cells and washing platelets in the USA. Conventional wisdom has been that calcium containing buffered solutions such as Ringer’s Lactate should not be used due to the potential risk of clotting in the citrate anticoagulated blood component, although this has been challenged.[4-6] Plasma-Lyte A, a buffered crystalloid, is approved by the USA Food and Drug Administration (FDA) as suitable for use with blood components but is rarely, if ever, used for this label indication. (personal experience) It is slightly more expensive. The FDA considers both normal saline and Plasma-Lyte A equally effective and safe for administration and dilution of transfused blood components according to the package inserts. Table 1 displays the biochemical makeup of normal saline and other common crystalloid solutions employed in the USA.

In recent years, the safety of normal saline has come into question in multiple settings, particularly in critically ill patients and for short term storage of red cells, including washing. Preliminary data suggest that normal saline causes dramatically higher levels of hemolysis than Plasma-Lyte A after washing and short term storage (24 hours or less). (M. Refaai, submitted for publication). [7] This may be important as it is now thought that even low levels of hemolysis may increase the risk of vital organ injury, vasculopathy, and predispose to nosocomial infection.[8-11] Levels of hemolysis which did not cause much concern previously, such as 50-100 mg/dL of cell-free hemoglobin, thought to be innocuous and frequently present in transfused red cells, may be harmful and are worthy of further

investigation. Of even broader concern for many clinical uses such as resuscitation and apheresis, is that large volume infusions of normal saline can cause hyperchloremic metabolic acidosis, which may impair renal function.[1-3, 12, 13] This review will address the literature on the risks of normal saline, and also suggest a research agenda for whether normal saline is truly, as long thought, the best solution for administering blood components and cell washing prior to transfusion.

Historical considerations

The testing that was required to allow use of normal saline with blood components is not easily discovered and it appears lost to the mists of time. Presumably, the lack of gross hemolysis was the most important criteria. Studies were performed on healthy animals, which may not be relevant to critically ill humans. In addition, there has been long standing debate about the use of colloids (e.g., albumin, hetastarch) vs. crystalloids for volume replacement in critically ill or injured patients. No real consensus exists, although a trend away from colloids and crystalloids towards use of blood components has been favored by American trauma surgeons and critical care physicians returning from our foreign wars. This has been supported by observational data demonstrating reduced edema and improved survival in young fit males seriously wounded in combat and resuscitated with blood components rather than traditional large volumes of crystalloid.[14]

Many critically ill patients do not need or receive red cells, platelets and plasma but do receive substantial amounts of crystalloid over the days or weeks in intensive care. Which fluid is most effective and safe? Opinions vary strikingly and no randomized trial data involving more than 2 liters of total infusion are available. The one randomized trial available found no significant differences in clinical outcomes with this volume of crystalloid.[15] Some anesthesiologists in the USA do not even stock normal saline in the operating room area, because of their preference for buffered solutions such as Ringer's Lactate and Plasma-Lyte A, and similar solutions such as Hartmann's are preferred in Europe and elsewhere. (personal communications) The studies comparing buffered crystalloid and normal saline have been recently reviewed.[12] It was concluded that acetate buffered solutions are superior physiologically to normal saline, but that key clinical questions of efficacy and safety remain unresolved. In particular, the relative beneficial versus deleterious effects of these resuscitation fluids on renal function remain inconclusive. The well known propensity for development of metabolic acidosis with normal saline is a serious disadvantage, likely due to the hyperchloremic and more modest hypernatremic content of normal saline. In general, the risks of fluid administration may have been underestimated overall.[16]

Animal models

The concept that balanced, buffered crystalloid solutions might be superior in efficacy and safety to normal saline is relatively recent, and has been addressed in only a few animal models. In rats with experimental hemorrhagic shock, resuscitated with either normal saline or Plasma-Lyte (an acetate and gluconate buffered crystalloid), rats receiving Plasma-Lyte had better renal blood flow and oxygenation, less acidosis, but there no differences in measures of inflammation and oxidative stress.[17] The same group used this model to

demonstrate improved renal blood flow and reduced acidosis with a combination of hydroxyethyl starch and buffered crystalloid compared with hydroxyethylstarch and normal saline.[18] Similar findings were observed in another rat model of hemorrhagic shock resuscitation, with Plasma-Lyte producing more rapid correction of acid base abnormalities and less intestinal injury when compared with either Ringer's Lactate or normal saline.[19]

In a rat model of sepsis resuscitation (cecal ligation and puncture), Plasma-Lyte produced less acidosis, better renal function and improved survival compared with saline.[20] In a control group of healthy animals who did not have sepsis, there was no difference in renal outcomes or survival between the two crystalloid solutions. In a sheep model of peritoneal sepsis, animals resuscitated with normal saline had more severe acidosis and lower cardiac output, inferior microcirculatory perfusion and inferior muscle oxygenation compared with animals receiving similar volumes of Lactated Ringer's or Plasma-Lyte. Survival was superior in those receiving Lactated Ringer's, compared to the animals receiving saline.[21]

***In Vitro* Studies of Biocompatibility of Normal Saline vs. Other Crystalloid Solutions**

It is a long-standing practice in blood banking in the USA to employ only normal saline to administer, dilute, or wash red cells and platelets. This is true despite the fact that Plasma-Lyte A, a more physiologic crystalloid, is FDA approved for compability with blood components for transfusion. In addition, multiple published studies now demonstrate that another long forbidden buffered crystalloid, Ringer's Lactate, does not cause clotting or hemolysis as has long been the conventional wisdom. [4-6] Other than lower cost, it is not clear why the USA transfusion medicine/blood banking community has insisted on use of a product more likely to cause metabolic acidosis (normal saline) over potentially safer solutions (e.g., Plasma-Lyte A; Ringer's Lactate), one of which is FDA approved for biocompatibility.

This traditional approach is particularly concerning since there are now abundant data suggesting that normal saline is more toxic, both *in vitro* and *in vivo*, in terms of tissue damage and hemolysis of red cells. For example, saline washing of red cells for neonatal extracorporeal membrane oxygenation recipients leads to increased hemolysis compared with unwashed red cells. [22] *In vitro* recent preliminary data demonstrate that normal saline washing is associated with a near doubling of hemolysis during the first 24 hours after washing, as compared with Plasma-Lyte A (Refaai, submitted for publication and abstract). [7] For use in intraoperative salvage with pre-infusion washing, a buffered solution containing mannitol, adenine and phosphate led to less red cell dysfunction and hemolysis than normal saline. [23] Plasma cell-free hemoglobin was four times higher with normal saline after four hours of storage, and reached levels (30 mg/dL) associated with organ injury in patients with sickle cell disease and other hemolytic disorders.[8-11] Similar results favoring buffered wash solutions were reported in salvaged blood washed with a bicarbonate-buffered hemofiltration solution as compared with normal saline. [24]

Lessons can be learned from the methods used for harvesting of other blood cells and tissues. Normal saline is never used in processing of human peripheral blood or marrow hematopoietic stem cells for clinical transplant in the USA. All processing is performed with Plasma-Lyte A due to concerns over effects on stem cell viability in acid, hyperosmolar,

unbuffered normal saline. Normal saline yielded inferior results to all other tested preservation solutions when employed for storage of human umbilical cord mesenchymal stem cells for transplantation.[25] Similarly, human saphenous vein grafts experienced increased graft injury, decreased viability and increased endothelial cell dysfunction when preserved for two hours in normal saline, and this damage was mitigated by use of buffered crystalloid solutions, including Plasma-Lyte A. [26]

Finally, in a preliminary report, short term *in vitro* exposure of sickle red cells to normal saline vs. phosphate buffered saline led to strikingly worse microvascular performance in microfluidic rheology assays. [27] The authors question whether normal saline should be avoided as a resuscitation fluid for sickle cell disease complications such as vaso-occlusive episodes and acute chest syndrome. Whether such results could be replicated with an FDA-approved buffered crystalloid solution such as Plasma-Lyte or Ringer's Lactate would be of great interest and an important area of future investigation.

Infusion of Normal Saline into Healthy Volunteers

A number of studies have compared infusions of normal saline with buffered crystalloids in healthy subjects. It has been known for decades that infusion of normal saline alters respiratory function in healthy subjects, with increased small airway resistance, increased angiopoietin-2 (a measure of inflammation), and increased interstitial pulmonary edema as measured by lung ultrasound.[28] In this instance 100 ml/minute of normal saline for a total bolus dose of 30 ml/kg was infused and compared with albumin or 5% glucose infusion in a randomised, double-blind trial. These adverse effects of normal saline were not observed with 4% albumin or 5% glucose solution.

In a sequential randomized trial of one-hour intravenous infusions of 50 ml/kg normal saline vs. Ringer's Lactate to healthy young subjects, normal saline resulted in decreased pH, subjective mental changes, abdominal discomfort and delays in first urination post infusion. [29] A similar study compared infusions of two liters of normal saline vs. Plasma-Lyte A over 1 hour and measured renal artery blood flow and renal cortical perfusion with MRI.[30] Compared with Plasma-Lyte A, normal saline led to reduced renal artery blood flow and cortical perfusion, hyperchloremia, and greater expansion of extravascular blood volume (the latter suggesting increased vascular permeability).

Finally, normal saline was compared with Plasma-Lyte A as pretreatment before intravenous propofol to determine the effects of fluids on propofol-associated infusion-site pain, in a blinded, randomized study. Normal saline increased pain, whereas Plasma-Lyte A mitigated the pain of propofol infusion in a dose dependent manner.[31] This finding is consonant with other data demonstrating vascular dysfunction and inflammation after normal saline infusion, as compared with buffered crystalloid.

Effects of Normal Saline Infusion in Patients Undergoing Major Surgery

Infusion of crystalloid in modest amounts is routine practice in almost all surgical patients undergoing major procedures. The administered volumes of crystalloid are greater in procedures associated with significant hemorrhage. Several randomized trials have demonstrated that normal saline leads to significantly greater metabolic derangements than

buffered crystalloids like Plasma-Lyte, particularly metabolic acidosis.[32-34] In one randomized trial of Plasma-Lyte 148 vs. normal saline in cardiac surgery, there were no differences in chest tube drainage, but the Plasma-Lyte recipients received more transfusions.[35]

A number of randomized trials have compared normal saline with buffered crystalloids in renal transplantation. For example, metabolic acidosis, severe hypotension requiring norepinephrine support, and hyperchloridemia were significantly more common in patients receiving normal saline compared with those receiving an acetate-buffered crystalloid (Elomel Isoton),[36, 37] although no differences in urine output or kidney function were observed. A meta-analysis confirmed worsening metabolic acidosis with normal saline compared to buffered fluids, and also demonstrated a non-significant trend toward higher graft loss and acute rejection in patients treated with normal saline.[38] Lastly, a recent study showed a significantly higher incidence of hyperkalemia requiring treatment following normal saline compared to buffered fluids.[39] In summary, no definitive evidence exists that use of buffered crystalloid solutions lead to lesser renal injury or graft dysfunction/loss than normal saline, but these data indicate greater metabolic derangements and suggest the possibility of increased vascular dysfunction with normal saline

Effects of Saline Infusion in Critically Ill Patients

Critically ill patients frequently receive many liters of crystalloid fluid during their hospital stay, thus the relative efficacy and safety of normal saline, the most frequently infused solution, is of particular importance in these recipients.

In a small (n=23) retrospective study of patients with diabetic ketoacidosis receiving solely Plasma-Lyte 148 vs. normal saline, the patients receiving Plasma-Lyte 148 had more rapid resolution of their acidosis, higher mean arterial blood pressure and better urine output than those patients who received only normal saline.[40] In a before and after intervention study, use of Hartmann's Solution or Plasma-Lyte 148 in the intervention period was compared with normal saline during the control period in a total of about 1,500 Australian ICU patients. This substitution of buffered crystalloid for normal saline therapy was associated with statistically significant reductions in serum creatinine, acute kidney injury and need for renal replacement therapy (10% vs. 6.3%), but no change in mortality or ICU length of stay. [41] In the largest randomized trial performed to date, 2,278 patients receiving either Plasma-Lyte 148 or normal saline had no significant differences in requirements for renal replacement therapy (there was a slight trend favoring normal saline) and a slight, non-significant trend (p=0.4) for lower mortality in the Plasma-Lyte 148 recipients (7.6% vs. 8.6%).[15] This study's major limitations were (1) the low risk status of the patients involved (e.g., the mortality rates are low—most patients were post-operative patients) and (2) the modest doses of crystalloid infused (approximately 2 liters).[42] A number of additional randomized trials are underway.[43, 44]

In a study involving trauma patients, Plasma-Lyte A caused less acidemia and hyperchloridemia compared to normal saline.[34] This study was not powered for clinical outcomes. A small subset of patients in this study demonstrated superior

thromboelastographic variables (K and alpha-angle) in trauma patients receiving Plasma-Lyte A as compared with normal saline.[45]

In a very large propensity-matched observational study based upon a multi-hospital database, septic ICU patients were treated with an median of 5 to 7 liters of normal saline or buffered crystalloids. The mortality was reduced in those receiving buffered crystalloids (RR 0.86; CI, 0.78, 0.94). Mortality was progressively reduced as the proportion of total crystalloid received that was buffered increased.[46]

Summary

There are extensive *in vitro*, animal model, and clinical data demonstrating that normal saline infusions contribute to undesirable metabolic changes including hyperchloremic metabolic acidosis, hyperkalemia and impaired renal function. For volume resuscitation of critically ill patients there seems no compelling rationale to use normal saline as a first choice.

As for *in vitro* use, red cells are adversely affected by short term exposure to normal saline, including increased hemolysis compared with buffered solutions such as Plasma-Lyte A. A research agenda for the future in transfusion medicine might include investigating whether or not normal saline contributes to hemolysis and cellular dysfunction after transfusion to patients. Hemolysis, even at low levels, may be deleterious to patients.[8-11] For red cell washing and red cell salvage, or during any exposure that can approximate 24 hours *ex vivo*, normal saline is inferior to Plasma-Lyte A. For these purposes, substitution of Plasma-Lyte A for normal saline seems warranted.

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Table 1

Characteristics of Typical Crystalloid Solutions

	Normal Saline	Lactated Ringer's	Plasma-Lyte A	Typical Healthy Human Serum/Plasma
pH (typical)	5.5	6.6	7.4	7.4
Osmolarity (mOsmol/L)	308	273	294	285
Sodium (mEq/L)	154	130	140	140
Chloride (mEq/L)	154	109	98	104
Calcium (mEq/L)	0	3	0	2.3
Potassium (mEq/L)	0	4	5	4
Magnesium (mEq/L)	0	0	3	1.5
Lactate (mEq/L)	0	28	0	Negligible
Gluconate (mEq/L)	0	0	23	Negligible
Acetate (mEq/L)	0	0	27	Negligible

Derived from USA package inserts approved by the Food and Drug Administration and UPMC clinical labs healthy controls

Table 2

Potential Disadvantages of Normal Saline as Compared with Plasma-Lyte A or other Buffered Crystalloid Solutions

<ul style="list-style-type: none">• Saline is more likely to cause metabolic acidosis• Saline is more likely to cause interstitial lung edema• Saline is more likely to cause renal blood flow disturbances• Saline is more likely to cause severe hypotension in renal transplant patients• Saline is more likely to cause hemolysis in washed and/or salvaged red cells for transfusion• Saline may be equivalent to other crystalloids in safety when 2 liters are administered to ICU patients