



Review:

0.9% saline is neither normal nor physiological

Heng LI^{§1}, Shi-ren SUN^{§2}, John Q. YAP³, Jiang-hua CHEN¹, Qi QIAN^{†‡4}

⁽¹⁾Kidney Disease Center, the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China)

⁽²⁾Division of Nephrology, Xijin Hospital, Fourth Military University College of Medicine, Xi'an 710032, China)

⁽³⁾Department of Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Rochester, MN 55905, USA)

⁽⁴⁾Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic College of Medicine, Rochester, MN 55905, USA)

†E-mail: Qian.Qi@mayo.edu

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Abstract: The purpose of this review is to objectively evaluate the biochemical and pathophysiological properties of 0.9% saline (henceforth: saline) and to discuss the impact of saline infusion, specifically on systemic acid-base balance and renal hemodynamics. Studies have shown that electrolyte balance, including effects of saline infusion on serum electrolytes, is often poorly understood among practicing physicians and inappropriate saline prescribing can cause increased morbidity and mortality. Large-volume (>2 L) saline infusion in healthy adults induces hyperchloremia which is associated with metabolic acidosis, hyperkalemia, and negative protein balance. Saline overload (80 ml/kg) in rodents can cause intestinal edema and contractile dysfunction associated with activation of sodium-proton exchanger (NHE) and decrease in myosin light chain phosphorylation. Saline infusion can also adversely affect renal hemodynamics. Microperfusion experiments and real-time imaging studies have demonstrated a reduction in renal perfusion and an expansion in kidney volume, compromising O₂ delivery to the renal parenchyma following saline infusion. Clinically, saline infusion for patients post abdominal and cardiovascular surgery is associated with a greater number of adverse effects including more frequent blood product transfusion and bicarbonate therapy, reduced gastric blood flow, delayed recovery of gut function, impaired cardiac contractility in response to inotropes, prolonged hospital stay, and possibly increased mortality. In critically ill patients, saline infusion, compared to balanced fluid infusions, increases the occurrence of acute kidney injury. In summary, saline is a highly acidic fluid. With the exception of saline infusion for patients with hypochloremic metabolic alkalosis and volume depletion due to vomiting or upper gastrointestinal suction, indiscriminate use, especially for acutely ill patients, may cause unnecessary complications and should be avoided. More education regarding saline-related effects and adequate electrolyte management is needed.

Key words: 0.9% saline, Hyperchloremia, Acidosis, Hyperkalemia, Balanced fluids, Renal hemodynamics

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1 Introduction

0.9% saline (sodium chloride (NaCl), henceforth referred to as saline) was first described by Dr. Har-told Jacob Hamburger (Dutch physiological chemist, 1859–1924) in the 1890s. Having a similar freezing point to human serum and causing no visible eryth-

rocyte lysis, the solution was initially named by Dr. Hamburger “indifferent fluid” (Awad *et al.*, 2014). Over the years, the name has morphed into what is more commonly called “normal saline” or “physiological saline” despite no additional evidence or rationale for the relabeling. The implied normalcy and physiological property have perpetuated indiscriminate use of saline in medical practice. Saline today remains one of the most frequently used solutions for resuscitation of acutely ill patients with a variety of medical problems.

To revisit some of the biochemical properties and clinical applications of saline would likely be

[‡] Corresponding author

[§] The two authors contributed equally to this work

ORCID: Qi QIAN, <http://orcid.org/0000-0002-1735-2657>

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beneficial because studies have shown that fluid and electrolyte management for most perioperative care has been left to junior house officers who lack sufficient knowledge and experience to undertake such a task. This problem was highlighted by a survey showing more than half of house officers did not know the amount of Na (likely unaware of high Cl content and low pH) in a liter of saline. Moreover, only 16% of surveyed house staff felt that they were adequately informed on the topic prior to or during their training (Lobo *et al.*, 2001; 2002b).

2 Saline is not physiological

Despite its name, saline is neither “normal” nor “physiological”. Compared to human serum, saline has a nearly 10% higher Na concentration and 50% higher Cl concentration. Table 1 shows the compositions of human serum, saline, and several commonly used balanced crystalloid fluids. The acidic property of saline (pH 5.4) can be clearly explained using the Stewart approach of acid-base balance which provides a perfect framework for its understanding (Stewart, 1983). The three independent determinates of circulating acid-base status are (1) strong ion difference (SID), (2) total concentration of nonvolatile weak acid (Atot), and (3) partial pressure of CO₂. Among the three, SID is the predominant determinate of pH. SID is defined as the difference of all fully dissociated cations (i.e. sodium, potassium, calcium, magnesium) and anions (chlorine, lactate, keto-acids, and all other organic anions with pK_a values <4.0). SID in normal serum (pH 7.35–7.45) is approximately 40 mmol/L (Fig. 1a). Isolated increases/decreases in SID move the acid-base equilibrium towards metabolic alkalosis/acidosis, respectively. In serum, increases or decreases in Atot (primarily albumin and phosphate) shift the equilibrium towards metabolic acidosis or alkalosis, respectively.

Saline has zero SID (equal concentrations of Na and Cl) and zero Atot. Intravenous saline infusion dilutes existing circulating albumin and phosphate, thus reducing Atot (metabolic alkalosis); simultaneously, the infusion reduces SID (metabolic acidosis). The effect of SID reduction, however, overpowers that of Atot reduction resulting in a net metabolic acidosis if there is no pre-existing acid-base disturbance (Fig. 1b). Thus, saline infusion in humans is expected to perturb the extracellular milieu, especially when large volumes are administered, causing hyperchloremia, which in turn has the potential to cause multiple downstream adverse effects.

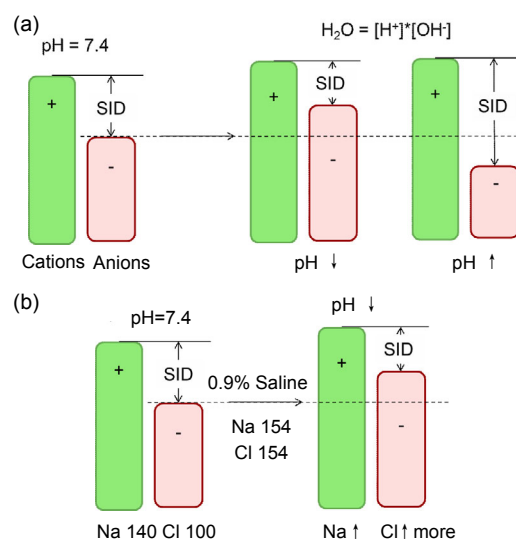


Fig. 1 Strong ion difference (SID) in normal circulation (a) and after 0.9% saline infusion (b)

(a) Based on the Stewart model, the difference between cations and anions in normal serum should be approximately 40 mmol/L (pH=7.4). SID decreases when negatively charged anions disproportionately increase compared to positively charged cations, resulting in a pH decline and acidosis. SID increases when anions disproportionately decrease, compared to cations causing pH elevation, metabolic alkalosis. (b) In normal serum, the predominant cation is Na (140 mmol/L) and predominant anions is Cl (100 mmol/L). The SID is approximately 40 mmol/L when pH is 7.4. 0.9% saline infusion causes elevations in both Na and Cl, but Cl increases in a larger magnitude, resulting in a net SID reduction and acidosis

Table 1 Comparison of normal serum, 0.9% saline, and balanced fluids

Solution	Na ⁺ (mmol/L)	K ⁺ (mmol/L)	Cl ⁻ (mmol/L)	Ca ²⁺ (mg/dl)	Mg ²⁺ (mg/dl)
Normal serum*	135–145	3.6–5.2	98–107	8.9–10.1	1.7–2.3
Saline	154	0	154	0	0
Lactated Ringer's (LR)	131	5.0	111	2.7	0
Hartmann's solution	129	5.0	109	4.0	0
Ringer's acetate (RA)	130	5.4	112	0.9	1.0
Plasma-Lyte	140	5.0	98	0	3.0

* Unit reference ranges from the Mayo Clinic

3 Hyperchloremia and hyperchloremic acidosis are abnormal

Cl, the most abundant anion in extracellular fluid, plays a fundamental role in the maintenance not only of acid-base balance but also of osmotic pressure, water distribution, and muscular activity in the body (Shires and Holman, 1948; Koch and Taylor, 1992; Powers, 1999; Yunos *et al.*, 2010). Studies have demonstrated that Cl is responsible for about a third of the extracellular fluid tonicity and two-thirds of all anionic charges in serum (Koch and Taylor, 1992). Because of its high concentration, Cl is the most important anion in balancing extracellular cations.

Hyperchloremic acidosis shifts potassium out of cells. Potassium is the most abundant intracellular cation with an intracellular concentration of approximately 140 mmol/L, and only approximately 2% of total body potassium is extracellular. Thus, even the slightest shift of intracellular potassium out of cells, a process directly proportional to the decline in pH, will exert a major impact on extracellular potassium concentration. Therefore, saline-induced acidosis can incite clinically significant hyperkalemia.

Hyperchloremic acidosis in healthy adults adversely affects the nitrogen balance because of the demand on the kidney to generate and excrete extra ammonia and inhibition of growth factor-mediated protein synthesis (Ballmer *et al.*, 1995). In a rodent sepsis model, hyperchloremic acidosis induces an increased concentration of circulating inflammatory mediators (interleukin-6, necrosis factor α , and interleukin-10) in a dose-dependent manner (Kellum *et al.*, 2006). Acidosis and inflammatory state can both compromise cardiac and skeletal muscle performance by reducing calcium sensitivity and maximal force generation (Fujita and Ishiwata, 1999; Morimoto *et al.*, 1999; Moopanar and Allen, 2005; 2006; Day *et al.*, 2006; 2007; Knuth *et al.*, 2006; Debold *et al.*, 2008; Snook *et al.*, 2008; Kapur *et al.*, 2009).

Uray *et al.* (2011) investigated the effects of saline (80 ml/kg) infusion on intestinal contractile function in rodents. The infusion caused intestinal edema and contractile dysfunction associated with activation of signal transducer and activator of transcription 3 (STAT-3) and sodium-proton exchanger (NHE) and decreased myosin light chain phosphorylation, along with alterations in cytoskeletal muscle

organization and F:G actin ratios. These saline-mediated effects could be related to both interstitial edema as well as hyperchloremic acidosis because the infusion volume is expected to induce hyperchloremic acidosis. Moreover, hyperchloremic acidosis caused by saline infusion in healthy volunteers has been shown to activate lymphocyte NHEs (Kessler *et al.*, 1997). Saline also exhibits a greater tendency of fluid retention in the interstitial space, compared to balanced crystalloids, causing edema, which is primarily related to a slow rate in excreting excess Cl by the kidneys (Veech, 1986). Thus pronounced interstitial fluid retention and hyperchloremia could be considered as convergent effects of saline infusion.

Cl channels are expressed in almost all cells in the body and appropriately circulating Cl concentrations are essential in maintaining cellular health. Cellular Cl alterations due to dysfunctions in Cl channels result in a broad spectrum of diseases (Puljak and Kilic, 2006; Veizis and Cotton, 2007; Tang *et al.*, 2010). Thus, conceptually, hyperchloremia caused by saline infusion cannot be viewed as normal.

4 Saline-induced pathological effects in humans

The biochemical differences between saline and human serum may have many notable clinical and pathological consequences. For example, in normal adults, compared to intravenous (IV) infusion of balanced fluids, saline infusion causes (1) multiple clinical symptoms including abdominal discomfort, abdominal distention and pain, nausea, drowsiness, decreased mentation and mental capacity; (2) disproportionate Cl elevation, leading to hyperchloremic metabolic acidosis; (3) a longer time to first micturition following the infusion; and, (4) less urine production (Scheingraber *et al.*, 1999; Williams *et al.*, 1999; Reid *et al.*, 2003). In addition, several randomized trials comparing saline with lactated Ringer's solution administered during the perioperative period have shown that the saline groups had a more frequent occurrence of adverse effects, including hyperkalemia (>6 mmol/L), more blood product transfusion and bicarbonate therapy (Ho *et al.*, 2001; Waters *et al.*, 2001; O'Malley *et al.*, 2005; Modi *et al.*, 2012).

Other clinical studies have shown that hyperchloremic acidosis resulting from saline infusion is associated with reduced gastric blood flow and mucosal pH in elderly surgical patients (Wilkes *et al.*, 2001), delayed recovery of gut function, increased complications, prolonged hospital stay in patients undergoing colonic surgery (Lobo *et al.*, 2002a; Brandstrup *et al.*, 2003), and impairment in cardiac contractility as well as diminished response to inotrope causing hypotension (Mitchell *et al.*, 1972; Levy *et al.*, 2010; Schotola *et al.*, 2012). Saline resuscitation for patients with gastrointestinal hemorrhage exacerbated bleeding resulting in more transfusions compared to balanced fluid resuscitation (Barak *et al.*, 2004). A large retrospective observational study involving 30 994 adults who underwent major open abdominal surgery showed that those who received saline had a significantly greater rate of developing complications, 33.7% versus 23% in those who received balanced fluids (Shaw *et al.*, 2012). Recently, Yunos *et al.* (2012) conducted a study to compare outcomes of critically ill adults resuscitated with Cl liberal (primarily saline) versus Cl restricted IV fluids. They showed that Cl liberal fluid was associated with significant increase in the development of Stage 2 or Stage 3 acute kidney injury compared to the patients receiving Cl restricted fluid. In the Mayo Clinic admission patients (in the years 2011–2013), post-admission (within 48 h) disproportionate serum Cl increase due to a high proportion of saline infusion was associated with an elevated risk of hospital mortality (unpublished data). Taken together, saline infusion can cause Cl elevation and can exert outcome significance for both healthy adults and acutely ill patients.

5 Pathological effects of saline on renal hemodynamics

Wilcox (1983) conducted a series of studies on anesthetized dogs that had one kidney auto-transplantation into the neck. Infusion of a hypertonic and NaCl-containing solution (two-thirds 0.154 mol/L NaCl solution and one-third 1.10 mol/L mannitol) to the renal artery resulted in hyperchloremia that was associated with persistent renovascular constriction (following a brief initial period of hyperosmolality

associated vasodilation) and reduction in glomerular filtration rate. The change in renal blood flow and the glomerular filtration rate is highly correlated with changes in fractional reabsorption of Cl, suggesting that renovascular resistance is related to the delivery of Cl, but not Na, to the Loop of Henle. Potassium has also been shown to induce renal vasoconstriction, which is dependent on and responsive to increased extracellular Cl (Jensen *et al.*, 1997; Hansen *et al.*, 1998).

This experimental evidence of the negative impact of saline on renal hemodynamics and kidney function is consistent with findings of renal perfusion impairment induced by saline infusion demonstrated by Chowdhury *et al.* (2012) in recent years. Using magnetic resonance imaging (MRI) techniques, Chowdhury and colleagues monitored, in real-time, renal blood flow velocity and renal perfusion in healthy adult volunteers following IV infusion of saline versus Plasma-Lyte 148 in a randomized double-blind cross-over design. When compared with Plasma-Lyte 148, saline infusion resulted in a significant decline in renal artery flow velocity and renal perfusion, and an increase in kidney volume consistent with tissue edema. Mechanistically, it is tempting to suggest that disproportionate Cl elevation from saline infusion increases Cl in the fluids of renal tubules, which can activate tubuloglomerular feedback (TGF) and cause afferent arteriolar vasoconstriction, leading to a fall in the glomerular filtration rate (Fig. 2). Studies from genetically engineered mice show that activation of high Cl-affinity NKCC (Na-K-2Cl co-transporter) isoform 2B and lower Cl-affinity NKCC isoform 2A is responsible for a wide range of NaCl concentrations in the tubular fluids over which TGF operates (Oppermann *et al.*, 2006; 2007).

The role of molecular densa in providing TGF to afferent vessels and signaling pathways leading to changes in renovascular constriction and glomerular filtration rate has been better elucidated recently (Ren *et al.*, 2004; Bell *et al.*, 2009). Cl entry to the molecular densa cells has been shown to cause depolarization to the basal lateral membrane via Cl channels (Bell *et al.*, 1989).

Moreover, kidney volume expansion following saline infusion can cause intra-renal regional tissue ischemia, as the kidneys have little room to expand

within the confines of the renal capsule. Interstitial edema induced by saline can cause subcapsular pressure elevation in the kidney and cause renal ischemia (Herrler *et al.*, 2010). The ischemia can induce regional activation of renin-angiotensin system (RAS), which increases proximal NaCl absorption and simultaneously enhances TGF activity causing further afferent arterial vasoconstriction (Mitchell and Navar, 1988) and reduction in the glomerular filtration rate (Mitchell and Navar, 1990). Mediators, which transmit the TGF signal from the macular densa cells to afferent arterioles, include adenosine working collaboratively with angiotensin II (Traynor *et al.*, 1998).

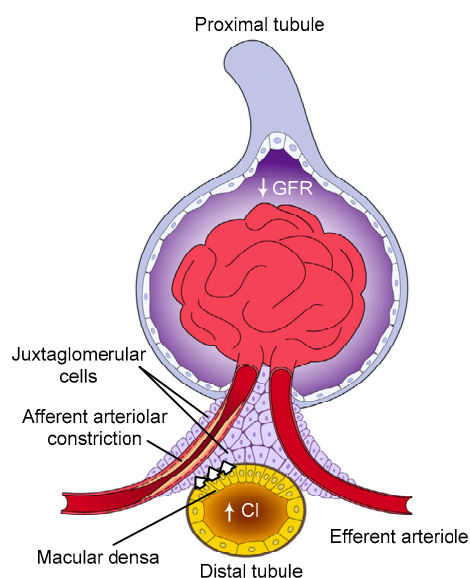


Fig. 2 A disproportionate increase in Cl and hyperchloremic acidosis caused by 0.9% saline infusion

The Cl filters into renal tubules. Through macular densa cells, the Cl signal is transmitted to afferent arterioles causing vasoconstriction, resulting in glomerular filtration rate (GFR) reduction and reduction in urine output. Regional ischemia due to saline-associated kidney volume expansion could further stimulate renin secretion from juxtaglomerular cells, leading to activation of the intra-renal renin angiotensin system (RAS). RAS activation would further enhance the proximal tubular Na absorption and afferent arteriolar vasoconstriction via tubuloglomerular feedback (TGF) activation

Both extra-renal pressure, such as ascites, and intracapsular pressure to the kidney can decrease the pressure gradient across the renal arterioles and result in decreasing renal blood flow and renal flow velocity. Improvement of urine output and kidney function has been demonstrated after release of the pressures (Stone and Fulenwider, 1977; Zand *et al.*, 2014).

6 Conclusions

Despite the availability of safer and more physiologically balanced solutions and despite not a single study demonstrating saline to be superior to balanced solutions, saline continues to be used frequently, if not the most commonly used resuscitative fluid, in medical practice. Evidence suggests that high Cl-containing fluids (such as saline) are associated with multiple adverse effects including an increased occurrence of kidney dysfunction with possible reduced survival. Although large randomized controlled trials comparing saline and balanced fluids are necessary, the time has come to at least recognize that saline is neither normal nor physiological. Saline administration should be considered to have the same status as a drug prescription. Strengthening knowledge of saline management would likely result in improvement in patient outcomes.

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Compliance with ethics guidelines

Heng LI, Shi-ren SUN, John Q. YAP, Jiang-hua CHEN, and Qi QIAN declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题目: 0.9%盐水既不正常也不生理

概要: 本文旨在客观评价 0.9%氯化钠溶液(盐水)的生物化学和病理生理学特性,并深入探讨静脉输注该盐水对机体酸碱平衡和肾脏血流动力学的影响。研究表明多数临床医生对电解质平衡的认识有限,对静脉输注盐水所引起的血浆电解质变化认识不足。而错误地应用盐水会增加患者的患病率和死亡率。健康成人剂量的(>2L)输注盐水会导致高氯血症并进而引起代谢性酸中毒、高钾血症和负氮平衡。总之,盐水是一种高度酸化的液体,用于治疗呕吐或上消化道减压引起的低氯性代谢性碱中毒和容量不足较为合适。临床上不加区分地应用盐水对患者特别是对重症患者可能导致不必要的并发症,应注意避免。临床医生对于盐水相关作用和电解质管理的认识亟需增强。

关键词: 0.9%氯化钠溶液(盐水); 高氯血症; 酸中毒; 高钾血症; 平衡液; 肾脏血流动力学