Chloride Conundrums

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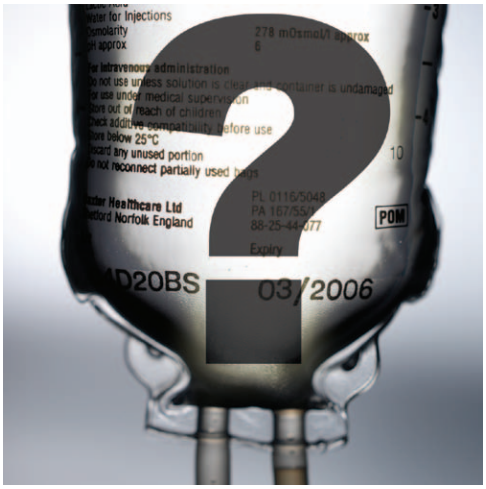
FOR years, there has been controversy over both the type and the amount of fluid patients should receive, especially for resuscitation in sepsis or septic shock. Recently, the debate has shifted from crystalloids *versus* colloids to whether "balanced" salt solutions (BSSs) are superior to 0.9% sodium chloride ("normal saline" [NS]) because of data linking adverse effects to the high chloride in NS. Lactated Ringer's solution (LR) and PlasmaLyte are commonly used BSSs, so named because their composition more closely resembles plasma, although lactate or acetate is added to permit near-normal concentrations of chloride. Two major concerns with the high-chloride concentration in NS are as follows: (1) large volume infusions or even just several liters infused rapidly in healthy individuals result in a nonanion gap metabolic acidemia because the high chloride in NS decreases the strong ion difference, although dilution of bicarbonate is an alternate, albeit less physiologic explanation[1,2]; and (2) hyperchloremia can produce vascular constriction, increase vascular reactivity to vasoconstrictors, and reduce renal perfusion, possibly causing acute kidney injury (AKI). Are the animal and human data sufficient to suggest curtailing the use of NS for resuscitation?



"…it does seem prudent, pending large prospective randomized studies, to use balanced salt solutions rather than normal saline, except in conditions in which normal saline would have a putative advantage…"

Many but not all animal models have shown that NS reduces renal blood flow compared with BSS. Hyperchloremia can cause renal vasoconstriction and a decrease in glomerular filtration that can be partly inhibited by indomethacin or a thromboxane synthetase inhibitor in animals.[3,4] Low chloride concentrations can also inhibit vasoconstrictor responses to arginine vasopressin, angiotensin II, and phenylephrine.[5] In contrast, renal blood flow did not differ with resuscitation using either PlasmaLyte or NS in rats subjected to hemorrhage, despite the persistence of the acidemia with NS.[6]

The study by Orbegozo *et al.*[7] in this issue of ANESTHESIOLOGY compared resuscitation with NS, PlasmaLyte, and LR in adult sheep in septic shock from intraperitoneal fecal instillation. It is exemplary in the use of elaborate fluid replacement protocols and multiple complementary forms of monitoring to determine systemic, renal, hemodynamic, and microcirculatory differences between these fluids. Survival, the primary outcome, was shorter in the NS group than in the LR group, whereas the survival of the PlasmaLyte group did not differ from either LR or NS. The expected acidemia occurred with NS, but also cardiac function and renal blood flow were reduced relative to the other two fluids. Various biochemical and physical measurements of microcirculation and ischemia also favored the LR and PlasmaLyte groups. Thus, this model provides convincing data that NS leads to greater cardiac depression and impaired perfusion of multiple vascular beds including the kidney relative to PlasmaLyte or LR in sheep. However, unlike humans with early septic shock,[8] and some ovine models,[9] the sheep were never hyperdynamic, although ovine and human genetic responses to lipopolysaccharide are similar.[10] Postresuscitation blood pressure was lower in the NS group due to a decreased cardiac output, with no differences in systemic vascular resistance. These findings along with a lower stroke volume are consistent with greater cardiac depression in the NS group that may have resulted from the acidemia rather than a direct effect of hyperchloremia. Unfortunately, the study lacked a power calculation and may have been underpowered for survival as the PlasmaLyte survival curve appears to be more similar to the NS curve, yet it was not statistically different from either the LR or NS curves. Also, renal blood flow was numerically but not statistically lower in the PlasmaLyte than the NS group after 20 h but did not differ statistically

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from the LR group, whereas NS did, which also suggests limited power.

In humans, production of a nonanion gap metabolic acidemia by NS is well documented, but data implicating NS in causing AKI are inconsistent and generally based on retrospective studies. An exception is a prospective comparison between 2 l of NS or PlasmaLyte infused during 2 h in healthy young men. In contrast to PlasmaLyte, NS was associated with a progressive decrease in renal artery blood velocity and cortical perfusion. Nonetheless, there was no evidence of renal damage in either group.[1] A widely cited before and after pilot performance improvement study found a decreased incidence of AKI using the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria class 2 (injury) and class 4 (injury and failure) after changing to a more frequent use of BSS.[11] However, aside from the issues inherent in this type of study design, there are multiple other limitations that preclude establishing a causal link between NS and adverse outcomes.[12] In contrast, a meta-analysis of high- *versus* low-chloride fluids in perioperative and critical care resuscitation found that mortality did not differ, but the incidence of AKI increased with high-chloride fluids.[13] However, this was not evident if only randomized studies were analyzed. Additionally, a 2013 Cochran Review of 14 clinical studies also could not demonstrate a difference in mortality or renal insufficiency between NS and BSS.[14] Interestingly, both historical and current guidelines for treating hyperosmolar hyperglycemic states, with or without ketoacidosis, suggest using NS for initial resuscitation. The large volume of NS required to treat these conditions might be expected to produce or exacerbate an acidemia and impair renal function, yet neither seems to be a clinical issue, although there is a paucity of studies.

Given the results of the study by Orbegozo *et al.*,[7] other animal data showing that NS impaired renal perfusion, the potentially adverse vascular effects of hyperchloremia, and the human data showing production of a metabolic acidemia and possibly other adverse vascular effects, why should not LR or PlasmaLyte be used in place of NS except for specific conditions, *e.g.*, hyponatremia or hypochloremia, as asserted by Butterworth and Mythen?[15] One potential disadvantage of LR is that although the calculated osmolality is about 273 mosm/l, the measured value is about 256 mosm/l because the activity of sodium in solution is only about 0.93. In contrast, the measured osmolalities of PlasmaLyte and NS are close to that of plasma. Thus, the use of LR in conditions in which hypoosmolarity is a concern, *e.g.*, cerebral edema may be problematic. Another concern is that the potassium in PlasmaLyte and LR might produce hyperkalemia, but this has not been borne out clinically. Favoring the continuing use of NS is the enormous experience with it for maintenance and resuscitation. Therefore, some of the adverse effects found in animal studies may not occur in humans or may be clinically unimportant or too subtle to detect clinically, especially in patients at high risk for complications. However, could the hypertension associated with salt intake be from the vascular effects of chloride rather than from the sodium, as commonly believed?

Because the study by Orbegozo *et al.*[7] adds another piece of convincing evidence that NS can have deleterious effects on both the heart and the vasculature in a model that resembles human sepsis in many ways, and because of suggestive, albeit not conclusive, human and other animal data, it does seem prudent, pending large prospective randomized studies, to use BSSs rather than NS, except in conditions in which NS would have a putative advantage, such as conditions in which hypoosmolarity may be an issue.

Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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