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EDITORIAL

# IV fluid choices in children: have we found the solution?☆,☆☆

## Escolhas de fluidos IV em crianças: encontramos a solução?

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There have been at least 15 randomized controlled trials (RCTs) published on the isotonic *versus* hypotonic maintenance fluid debate in the last decade, the most recent of which was the trial conducted by Valadão et al.,[1] published in this issue of *Jornal de Pediatria*. Based on a concern that children undergoing surgery are at particular risk of hospital-acquired hyponatremia, these investigators conducted a single center, double-blinded RCT comparing isotonic (150 meq/L or essentially a 0.9% NaCl solution) to a 30 meq/L (0.2% NaCl) hypotonic solution in children undergoing appendectomy, from the time of admission until 48 h post-operatively. With a total of 50 patients included in their per protocol analyses (23 and 27 in each arm, respectively), the authors did not find any statistically significant difference in serum sodium in both groups at 24 or 48 h. They also did not observe any differences in the secondary outcomes of hypervolemia and other electrolyte disturbances. The authors therefore concluded that both hypotonic and isotonic solutions are appropriate for maintaining intravenous fluid choices in children undergoing appendectomy.

The history of the debate around the most appropriate choice of intravenous maintenance fluids in children evolved from concerning case reports and observational studies in the 1990s, which fueled opinion-based narrative reviews in the early 2000s, suggesting a harmful potential for significant hyponatremic encephalopathy and mortality with hypotonic fluids.[2] Those in favor of isotonic solutions argued that fluids containing higher sodium (and therefore tonicity) reduce the risk of iatrogenic hyponatremia and its sequelae in the setting of an inability to excrete free water,[3] while those in favor of hypotonic solutions argued that iatrogenic hyponatremia is related to excess fluid volume administration, and not a dilutional effect of free water intake, and that isotonic fluid increases the risk of hypernatremia.[4] The conclusions of experts in the field at that time were invariably a call for more rigorous, prospective evidence in this important area before more definitive recommendations on safe fluid practices could be made.[5,6] Subsequently, an increasing number of RCTs and at least six systematic reviews and meta-analyses published over the last ten years later have provided a higher grade of evidence to end this debate.[5,7–10] The findings and conclusions of this body of evidence have been consistent. Compared to hypotonic maintenance fluids,

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isotonic solutions significantly reduce the risk of iatrogenic hyponatremia, particularly in the first 24 h of administration, with some evidence that this effect persists at 48 h.[10,11] Isotonic solutions protect against hyponatremia without an increased risk of hypernatremia in both medical and surgical patients, as well as in critically and non-critically ill children.[10,12] While there are fewer trials comparing the effect of fluid volume *versus* tonicity intake, the evidence to date also suggests that iatrogenic hyponatremia is related to the maintenance solution tonicity, rather than volume.[13] In other words, restricting hypotonic fluid intake does not protect against hyponatremia when compared to isotonic solutions. In fact, restricting the volume of isotonic fluid intake, while it reduces the risk of hyponatremia, may not prevent its occurrence.[11] Since the Cochrane review on this subject, which was published in December of 2014 and included a total of 10 RCTs in 970 children, five new RCTs were published, in addition to the trial by Valadão et al.,[1] enrolling over 1100 patients.[11,12,14–16] The number of children enrolled in clinical trials comparing hypotonic to isotonic fluids has more than doubled in the last year, and continue to strengthen the evidence in favor of isotonic maintenance solutions. Contrary to the original recommendations of Holliday and Segar and to the concerns proposed earlier,[4] isotonic fluids were proven to be safe and were associated with a reduction in the risk of hospital-acquired hyponatremia. It has been suggested that this reduction in risk may in fact be underestimated, as many studies to date excluded patients with baseline hyponatremia.[8]

Why are the results of Valadão et al.'s trial[1] contrary to this evidence? While the authors conclude that their results suggest there is no increase in risk with either fluid type, we caution against this interpretation due to their sample size. This was a small study that was not powered for the stated primary outcome. There were three and four withdrawals in each arm; as this was not an intention to treat analysis, it is unclear the impact that this had on the results. A difference between groups may not have been detected as the timing of serum sodium measurements was 24 and 48 h after surgery (not intervention), and hyponatraemia is most commonly reported within 24 h of intervention.[10,12] Both arms also received a significant amount of isotonic fluids pre- and intra-operatively, which potentially diluted their ability to detect a difference in serum sodium. Comparing mean serum sodium in this small sample, as opposed to the incidence of hyponatraemia, may not be the most appropriate outcome to assess the safety of hypotonic *versus* isotonic fluid, given a regression to the mean bias.[17] The only significant difference detected between both groups is the higher preoperative fluid balance in the hypotonic group; the authors suggest that this contributed to hyponatremia at baseline. However, as the intervention duration was 48 h after surgery, and their data showed no difference in the post-operative fluid intake or balance, this observation may have been due to chance.

While serum sodium was not significantly different in the two groups, hyponatremia did develop in a number of patients after exposure to hypotonic as well isotonic fluids, and in patients who were normonatremic at baseline. It is important to note that half ($n = 24$) of the participants in this trial were hyponatremic at baseline, of whom 15 (62.5%) normalized their serum sodium during the study period, regardless of the administered solution. However, the proportion of patients with hyponatremia in each group at baseline is unclear. This illustrates that sodium balance is not simply influenced by sodium intake and tonicity of maintenance intravenous fluids, but is multifactorial. Possible responsible mechanisms include the dilutional effect of a positive balance of free water either from administration, and/or and impaired ability to excrete free water as a result of non-osmotic antidiuretic hormone (ADH) excretion, and translocational hyponatremia with increased osmolar gap.[18] Unfortunately, this study did not include measurements of ADH, urine osmolality, and electrolytes, not allowing for a full explanation of the possible mechanisms for the observed results.

While we commend the authors on conducting this trial, we caution readers against concluding that, based on the lack of demonstrable difference, hypotonic solutions are *as safe as* isotonic solutions. The overwhelming prospective evidence to date indicates that isotonic maintenance solutions are *safer* than hypotonic fluids in protecting against hospital-acquired moderate and severe hyponatremia in medical and surgical pediatric patients. If hyponatremia was purely a problem of dilution, then all hypotonic solutions should be abandoned. While isotonic fluid is not the only solution for correcting low sodium, it is certainly the safest empiric choice. Concerns regarding the potential for harm associated with intravenous fluid containing less than 77 mmol/L, together with an accumulating wealth of prospective clinical trial evidence has resulted in a practice change and amended national clinical guidelines.[19] Our next debate is which isotonic fluid is superior, a balanced salt solution or 0.9% NaCl.[20] Studies to date have not evaluated the potential for hyperchloremic metabolic acidemia when isotonic fluids are administered at maintenance rates. This is a well-recognized sequelae of volume expansion with 0.9% saline, and a growing concern given its potential association of morbidity and mortality in the critically ill population.[21] We emphasize that there is no ideal single solution that can guarantee correction of electrolyte abnormalities. Individualizing fluid prescriptions according to the patient's physiology, vigilance with monitoring, and dose adjustment of fluid composition and volume according to therapeutic endpoints are key components to safe intravenous fluid practices in children.

## Conflicts of interest

The authors declare no conflicts of interest.

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