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EDITORIAL COMMENTARY

Isotonic versus hypotonic intravenous maintenance fluid therapy: what's new?

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Intravenous maintenance fluid therapy (IV-MFT) is routinely used for hospitalized children with reduced oral intake in various clinical conditions to preserve extracellular volume [1]. Hypotonic fluids containing 30 to 50 mmol/L of sodium have been traditionally used for IV-MFT, which was based on daily requirements of water and electrolytes described by Holliday and Segar [2]. However, a number of literatures have described case series of deaths secondary to hyponatremia associated with the use of hypotonic fluids [3–5]. Because the Holliday–Segar formula was developed based on weight, energy expenditure, and physiologic losses in healthy children [2], it is obvious that the formula does not apply to all hospitalized children. Acutely ill children often have clinical symptoms such as fever, nausea, vomiting, seizure, and respiratory distress, all of which can cause non-osmotic antidiuretic hormone (ADH) secretion, resulting in water retention and dilutional hyponatremia [6]. When children in these conditions receive electrolyte-free water such as hypotonic saline, they can develop hospital-acquired hyponatremia.

Many randomized controlled trials (RCTs) have been conducted to compare isotonic fluids and hypotonic fluids in IV-MFT, and most studies have described that hypotonic fluids have a higher risk of hospital-acquired hyponatremia [7–9]. Several systematic reviews and meta-analyses have been conducted, concluding that isotonic fluid would be a safer choice for IV-MFT [10–15]. The American Academy of Pediatrics and the National Institute for Health and Care Excellence have also recommended the use of isotonic fluids for routine IV-MFT [1, 16].

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However, several researchers have described that there remains a wide variety of choices for IV-MFT in daily practice [17, 18]. Additionally, a number of RCTs have been conducted after the last meta-analysis by Hasim et al. [15], and several studies showed no difference in hyponatremia between isotonic and hypotonic fluids [19–21].

In the article "Efficacy and safety of isotonic versus hypotonic intravenous maintenance fluids in hospitalized children: an updated systematic review and meta-analysis of randomized controlled trials," Amer et al. provided updated recommendations for IV-MFT based on all published RCTs [22]. Accordingly, it is the most comprehensive meta-analysis, including 33 studies and 5049 patients [22]. In terms of hyponatremia, isotonic fluid was superior to hypotonic fluid, which was consistent with all previous studies [10–15]. They also performed subgroup analysis based on the duration of fluid interventions, which was analyzed in only two previous meta-analyses [10, 15]. As a result, isotonic fluid had a lower risk of mild to moderate hyponatremia at both ≤ 24 and > 24 h. Additionally, isotonic fluid significantly decreased the risk of severe hyponatremia after 24 h but not ≤ 24 h, highlighting the superiority of isotonic fluid for longer durations of fluid therapy. In contrast, hypotonic fluid had significantly lower serum sodium and chloride levels and lower serum osmolarity compared to isotonic fluid at ≤ 24 h but not at > 24 h [22]. The authors speculate that the improvement of patients with therapy results in fewer non-osmotic ADH stimuli and, consequently, less water retention and lesser changes in serum osmolarity and electrolytes [22]. The discrepancy of these two findings (increased risk of severe hyponatremia only after 24 h and lower sodium level and lower osmolarity in only ≤ 24 h) was not discussed. One explanation may be that a small group of patients may continue to suffer symptoms which can cause non-osmotic ADH secretion, resulting in aggravation of hyponatremia, while in the majority of patients symptoms relieve quickly with improvement of electrolyte abnormalities.

The meta-analysis conducted by Amer et al. also showed that isotonic fluid significantly increased the risk of hypernatremia at ≤ 24 h compared to hypotonic fluid [22]. However, the sensitivity analysis excluding trials conducted on neonates showed that the risk of hypernatremia became insignificant [22]. This process seems to be reasonable, because neonates differ from other children in their renal handling of body fluids and electrolytes [23].

Of interest, isotonic fluid significantly increased serum creatinine at ≤ 24 h [22]. This is the first meta-analysis to perform subgroup analysis based on the composition of the isotonic fluid (i.e., balanced versus 0.9% saline), and showed that 0.9% saline was associated with significant increase in serum creatinine level. There was no significant difference between isotonic and hypotonic groups in studies which used balanced isotonic solutions [22]. 0.9% saline contains supraphysiological concentrations of chloride that can induce or exacerbate hyperchloremia and metabolic acidosis, which may cause renal vasoconstriction and decreased glomerular filtration rate [24, 25]. The use of 0.9% saline has been shown to significantly increase serum chloride and decrease serum bicarbonate even in adult patients: however, without differences in mortality and kidney failure when compared to balanced crystalloids [26, 27].

Subgroup analysis based on different regions of the included studies revealed another interesting finding. Although isotonic saline significantly decreased the risk of hyponatremia in studies conducted in Asia, Australia and Oceania, and Europe, there was no significant difference between the two fluids in terms of mild hyponatremia in studies conducted in both North and South America [22]. There may be differences in fluid management practice, types of used fluids, or patients' underlying conditions between America and other areas. Further studies are required to understand this difference.

There was a trend that isotonic fluid had a higher risk of edema and death compared to hypotonic fluid, although statistical significance was not reached [22]. For this reason, caution about the risk of volume overload is required when isotonic fluid is used.

There are several limitations regarding the meta-analysis of IV-MFT. First, studies are heterogeneous in terms of electrolyte compositions, maintenance rates, and medical and surgical conditions. Second, a two-arm group was combined to compare with the other group, which may cause bias as the fluids differ in their tonicity or rate of administration. Third, a fluid bolus prior to maintenance IV-MFT, which may affect serum sodium concentration, is not considered. Despite all these limitations, the results were maintained in most subgroup analyses, indicating that the findings can be generalized in a wide range of settings [22].

What does this meta-analysis add after all? Isotonic fluid reduces the risk of hospital-acquired hyponatremia, which is concordant with all previous meta-analyses. A new insight is that balanced isotonic solutions may be a preferable choice for IV-MFT in selected patients with severe metabolic acidosis at admission to avoid the potential risk of kidney dysfunction and significant decrease of blood pH. Surprisingly, there were no differences in serious adverse events between isotonic and hypotonic fluids. We can speculate that this may depend on the low frequency of severe complications such as significant hyponatremia. It has been recommended that plasma electrolyte concentrations and blood glucose should be measured at initiation of IV-MFT and at least every 24 h thereafter, and subsequent IV-MFT should be based on the plasma electrolyte and blood glucose measurements [16]. However, this is not always possible in some developing countries. For this reason, 0.9% saline may be a safer option where health resources are limited.

An important issue remains the electrolyte concentration in the maintenance fluid solutions for newborns and infants in the first months of life. Well-designed studies are needed in this field.

Eventually, IV-MFT should be treated like any other drug and used with careful attention to all potential risks, including iatrogenic hyponatremia and volume overload.

Declarations

Conflict of interest The authors declare no competing interests.

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