Pediatr Nephrol (2015) 30:1163–1172
DOI 10.1007/s00467-014-3033-y

ORIGINAL ARTICLE

Isotonic versus hypotonic saline solution for maintenance intravenous fluid therapy in children: a systematic review

April P. Padua · Josep Ryan G. Macaraya · Leonila F. Dans · Francisco E. Anacleto Jr.

Received: 18 January 2014 / Revised: 28 November 2014 / Accepted: 5 December 2014 / Published online: 11 January 2015

Abstract
Background The administration of hypotonic saline solution for maintenance intravenous fluid (IVF) therapy has been the standard of care, but recent evidence has shown this treatment to be associated with hyponatremia-related complications. The aim of this systematic review was to determine which IVF, i.e., a hypotonic or an isotonic saline solution, poses less risk for the development of hyponatremia among hospitalized children who require maintenance IVF therapy.
Methods Medline, Cochrane Library, LILACS, Current Controlled Trials, reference lists, and abstract proceedings were searched for randomized controlled trials (RCTs) comparing hypotonic and isotonic saline solutions for maintenance IVF therapy in hospitalized children. Two reviewers independently assessed all potentially relevant studies and subsequently extracted data and evaluated the methodological quality of the RCTs. Studies were then combined and analyzed using a random effects model.
Results Eleven RCTs met the inclusion criteria. Our analysis of these 11 RCTs showed that among hospitalized children receiving maintenance IVF therapy, isotonic solutions significantly decreased the risk of developing hyponatremia [relative risk (RR) 0.50, 95 % confidence interval (CI) 0.40–0.62] without significantly increasing the risk for hypernatremia (RR 0.83, 95 % CI 0.41–1.67).
Conclusions Current evidence does not support the standard practice of prescribing a hypotonic saline solution as maintenance IVF therapy to hospitalized children. Although there is no single IVF composition ideal for all children, an isotonic saline solution does appear to be the safer choice when maintenance IVF therapy is used in the general pediatric population.

A. P. Padua (✉) · J. R. G. Macaraya · L. F. Dans · F. E. Anacleto Jr.
Department of Pediatrics, University of the Philippines Manila–Philippine General Hospital, Manila, Philippines
e-mail: appadua1@up.edu.ph

Keywords Isotonic saline · Hypotonic saline · Intravenous fluid therapy · Hyponatremia · Pediatric patient population

Introduction

Hyponatremia, defined as a plasma sodium (pNa) concentration of<135 mmol/L, is the most common electrolyte abnormality seen in hospitalized children [1]. The initial symptoms, including headache, nausea, and general malaise, are nonspecific, making early recognition difficult and depending on severity, patients may subsequently develop seizures and progress to coma and even death [2].

Since the 1980s, there have been more than 50 reports of death or permanent neurologic injury secondary to hyponatremic encephalopathy [3]. This condition has received much interest due to a steady accumulation of evidence in recent years of its association with the use of hypotonic maintenance intravenous fluids (IVF), a therapy that has been the standard of care since the publication of Holliday and Segar's study in 1957 [4]. However, according to some researchers, Holliday and Segar's recommendations may not be applicable to hospitalized children because they do not take into account the effect of anti-diuretic hormone (ADH) released in response to various hemodynamic and non-hemodynamic stimuli [5]. In light of these recent developments, isotonic fluids, such as 0.9 % sodium chloride (NaCl), have been advocated as the more appropriate maintenance IVF, and hypotonic solutions are now reserved for patients with either hypernatremia or ongoing urinary or extra-renal free water losses [6].

Since 2006, several published systematic reviews have compared the use of isotonic and hypotonic maintenance IVF in hospitalized children, with the majority concluding that isotonic IVF is safer than hypotonic IVF in terms of the risk of developing hyponatremia [2, 7–11]. However, a

general consensus within the pediatric community has yet to be established. Hence, we have conducted a systematic review of the use of isotonic or hypotonic maintenance IVF in hospitalized children which includes randomized controlled trials (RCTs) that were not included in earlier reviews. Our aim is to provide more clarity on this issue.

Methods

A number of electronic databases [MEDLINE®/PubMed® (1966–2013); Cochrane Central Register for controlled trials (CENTRAL) published in The Cochrane Library; LILACS (1982–2013); Current Controlled Trials (CCT)] were searched for appropriate published studies using the search terms "hypotonic solution," "isotonic solution," "fluid therapy," "randomized controlled trial," and synonyms or related terms. To search for unpublished studies, we accessed the following online databases: WHO Network of Collaborating Clinical Trial Registers; Clinical-Trials.gov (U.S. National Institutes of Health); U.S. Food and Drug Administration (FDA) Registry; International Committee of Medical Journal Editors (ICMJE) Registry. Abstracts from relevant scientific forums, such as the Society for Pediatric Research, Critical Care Congress, and American Academy of Pediatrics, were reviewed. Hand searching of reference lists of identified articles was also done. Experts in the subject were consulted as well.

Two reviewers (AP and JM) independently screened the titles and abstracts of articles that were identified through the systematic literature search. Full-text articles of potentially relevant studies were then retrieved and assessed independently by both reviewers using the following inclusion criteria: (1) the study design was a RCT; (2) hospitalized children aged 1 month to <19 years old who received maintenance IVF therapy were enrolled in the study; (3) the study compared the use of isotonic or near-isotonic IVF and hypotonic IVF. An IVF is classified as isotonic if it approximates the effective osmolality of plasma—that is 154 meq/L of sodium + potassium (e.g., 0.9 % NaCl, Hartmann's solution, lactate Ringer's solution, or Normol-R solution)—and as hypotonic if its osmolality is lower than the effective plasma osmolality (e.g. 0.18–0.45 % NaCl, Normol-M solution) [12]. Studies which were non-RCTs and which had enrolled patients who were hemodynamically unstable, had conditions associated with dysnatremia (e.g., congestive heart failure, renal disorder, liver failure), or required fluid resuscitation or fluid replacement therapy were excluded.

Our primary outcome was the proportion of patients who had hyponatremia (pNa<135 mmol/L) within 48 h from the initiation of maintenance IVF therapy. Other outcomes of interest were classified into patient-centered outcomes (mortality, neurologic sequelae, clinical evidence of volume overload) and laboratory outcomes (severe hyponatremia, defined as pNa<130 mmol/L; hypernatremia, defined as pNa>145 meq/L).

Data on the methodological quality and clinical characteristics of the included trials were extracted independently and in duplicate by both review authors. In cases of differences in opinion, a third author was consulted. The Cochrane risk-of-bias tool was used to assess risk of bias in the included trials. Domains that were assessed included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting [13].

Statistical analysis was conducted using Review Manager Software (RevMan ver. 5.2; The Cochrane Collaboration, Oxford, UK). For factorial trials, multiple intervention groups were combined in order to create a single pairwise comparison (i.e., isotonic vs. hypotonic IVF). Intervention effects were pooled and analyzed using the random effects model. For dichotomous outcomes (e.g., occurrence of hyponatremia or hypernatremia), risk ratio (RR) and 95 % confidence intervals (CI) were used. For continuous outcomes (e.g., pNa level), the weighted mean difference (MD) and 95 % CI were used. Heterogeneity was evaluated using the Chi-square test (χ^2) statistic and was deemed significant if the p value was ≥0.10. Where statistical pooling could not be done, the findings were described qualitatively.

Authors were contacted if necessary in order to request unreported data. However, when data were not collected in a certain study or were not available, only the available data were used in the analysis. Imputation for missing data was not done. In cases where medians were the only available data, standard deviations were derived from the p value [13].

Subgroup analysis was decided a priori to investigate the effects of age (<1 year old, 1–5 years old, >5 years old), condition (medical vs. surgical), and rate at which IVF was administered (full maintenance rate vs. restricted rate, defined as ≤2/3 of full maintenance rate).

Post-hoc analysis was done to determine the effect of maintenance IVF therapy with an isotonic versus a hypotonic saline solution on mean pNa level and a drop in the pNa level.

Results

Results of the search of electronic and online databases

A flow diagram of selection of studies included in this systematic review is shown in Fig. 1. Ultimately, 11 RCTs which compared the use of isotonic versus hypotonic maintenance IVF in hospitalized children were included in this systematic review.

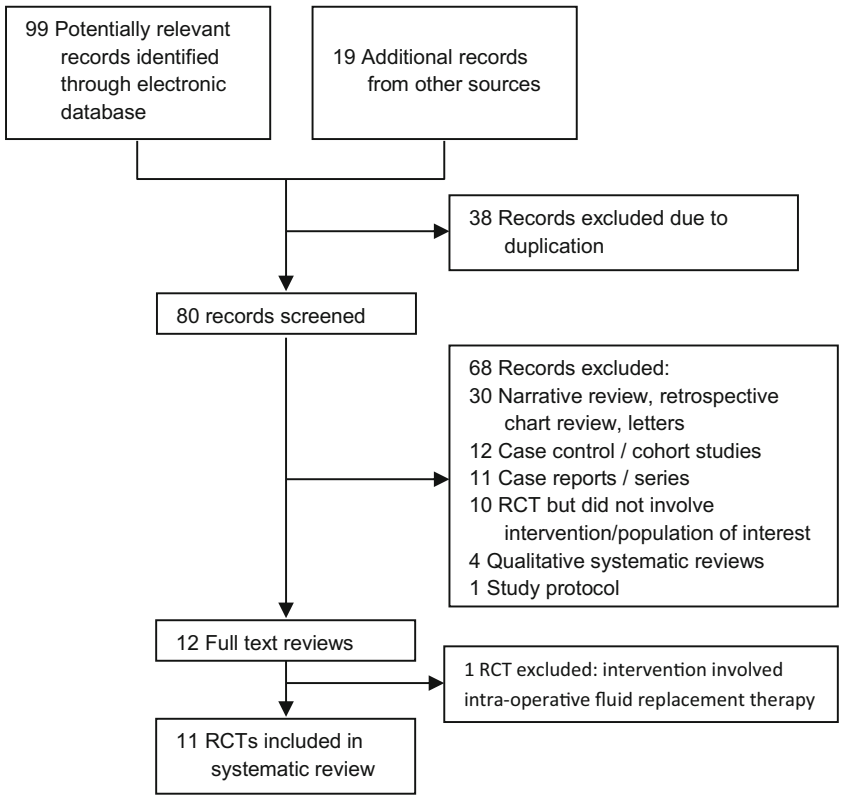

Fig. 1 Flow diagram of selection of studies included in the systematic review. *RCTs* Randomized controlled trials

Study characteristics

Eleven RCTs were included in the meta-analysis, with a total patient enrolment of 1,095 children, aged 3 months to 18 years old. Of these 1,095 children, 530 were allocated to the intervention group (isotonic IVF group) and the remaining 565 were allocated to the control group (hypotonic IVF group). Characteristics of these studies are given in Table 1.

Five of the RCTs included in our systematic review enrolled surgical patients only [14–18], one trial included medical patients only[19], and the remaining five RCTs enrolled both surgical and medical cases [20–24]. In general, children randomized to the intervention group mostly received D5 0.9 % NaCl (6/11 RCTs) [19, 14, 15, 20–22]. There was more variability in the choice of hypotonic solution used across studies, the most common of which was D5 0.45 % NaCl (5/11 RCTs) [14, 15, 20, 21, 16].

Risk of bias

A detailed summary of the methodological quality of each included RCT is shown in Table 2. Of the 11 RCTs, one trial had insufficient information on the sequence generation process used [17], while three trials did not describe their method of allocation concealment [17, 18, 23]. Only four RCTs were double-blinded [14, 20–22], one was single-blinded (i.e., only participants and caregivers were blinded) [16], while the majority were open-label (i.e., participants, caregivers, and personnel were not blinded) [19, 15, 17, 18, 24]; one RCT did not describe the blinding procedure used [23]. All RCTs were low risk for detection bias since the outcome measurement (i.e., determination of pNa level) is not likely to be influenced by lack of blinding of outcome assessors. Several RCTs excluded >10 % of their initial study population in their analysis, mostly due to the attending physician's early discontinuation of IVF [14, 15, 21, 18, 23]. Three of these RCTs were judged to be at high risk for attrition bias either because a significant proportion of the study population's outcome was missing [14, 23] or there was no mention of intention-to-treat analysis [21]. Only one RCT was judged to be at high risk for selective reporting because the authors only reported mean change in pNa without reporting mean pNa levels and the proportion of patients who actually became hyponatremic [22].

Laboratory outcomes

Our analysis showed that the use of isotonic maintenance IVF significantly reduced the risk of developing hyponatremia (10 studies, 1,006 participants, RR 0.50, 95 % CI 0.40–0.62) (see Fig. 2) and severe hyponatremia (8 studies, 845 participants, RR 0.21, 95 % CI 0.10–0.45) (see Fig. 3). Although Kannan et al. [19] defined hyponatremia as a pNa level of<130 mmol/L, they re-analyzed their data using pNa <135 mmol/L as their

Table 1 Characteristics of the 11 studies included in the systematic review

First author/year of study	N[a]	Condition[b]		Follow-up period (h)	Experimental group (isotonic IVF)		Control group (hypotonic IVF)	
		Surgical	Medical		Age[c] (years)	IVF	Age[d] (years)	IVF
Brazel/1996 [17]	12	12 (100)	–	≤72	Adolescent	Hartmann's solution	Adolescent	0.3 % NaCl, 3 % D 0.18 % NaCl, 4 % D
Montanana/2008 [18]	103 (122)	122 (100)	–	6–24	3.2 (1.3, 10.0)	Na 140 meq/L, K 15 meq/L, 5 % D	3.0 (0.9, 7.0)	Na 20–100 meqs/L, 5 % D
Ang/2008 [24]	19	4 (21)	15 (79)	24	7.0±6.1	D5NR[d]	8.9±5.9	D5NM[e]
Yung/2009 [22]	28 (30)	19 (68)	11 (32)	12–24	5.3 (0.9; 12)	0.9 % NaCl (2/3 FM)	4.7 (1.4, 8.9)	0.18 % NaCl, 4 % D (2/3 FM)
	22 (24)	18 (82)	4 (18)	12–24	15.4 (10.8, 15.9)	0.9 % NaCl (FM)	3.7 (1.5, 14.7)	0.18 % NaCl, 4% D (FM)
Kannan/2010 [19]	167	–	167 (100)	12–72	3.0 (1.0, 7.0)	0.9 % NaCl, 5 % D (FM)	4.0 (1.1–6.0)	0.18 % NaCl, 5 % D (FM) 0.18 % NaCl, 5 % D (2/3 FM)
Neville/2010 [15]	62 (74)	74 (100)	–	8–24	9.4 (1.0, 14.9)	0.9 % NaCl, 5 % D (50 % FM)	9.9 (2.0, 15.0)	0.45 % NaCl, 5 % D (50 % FM)
	62 (74)	74 (100)	–	8–24	8.4 (0.6–14.9)	0.9 % NaCl, 5 % D (FM)	9.1 (0.9, 14.9)	0.45 % NaCl, 5 % D (FM)
Choong/2011 [14]	218 (258)	258 (100)	–	12–72	9.2±5.5	0.9 % NaCl, 5 % D	9.2±5.7	0.45 % NaCl, 5 % D
Rey/2011 [23]	125 (134)	57 (46)	68 (54)	12–24	4.9 (2.0, 10.6)	136 mmol/L NaCl, 20 mmol/L KCl	4.7 (1.7, 9.9)	30–50 mmol/L NaCl, 20 mmol/L KCl
Saba/2011 [21]	37 (59)	25 (68)	12 (32)	8–18	8.2 (2.8, 14.3)	0.9 % NaCl,5 % D	8.9 (1.7, 16.5)	0.45 % NaCl, 5 % D
Coulthard/2012 [16]	79 (82)	82 (100)	–	16–18	11.3 (4.3, 13.9)	Hartmann's solution, 5 % D (FM)	11.5 (6.0, 14.1)	0.45 % NaCl, 5 % D (2/3 FM)
Baron/2013 [20]	63	7 (63)	56 (37)	24–48	0.4 (0.2, 0.8)	0.9 % NaCl, 5 % D	0.4 (0.2, 0.8)	0.45 % NaCl, 5 % D

IVF, Intravenous fluid; NaCl, sodium chloride; D, dextrose; LR, lactated Ringer solution; KCl, potassium chloride; FM, full maintenance rate; D5NR, 5 % Dextrose Normosol-R; D5NM, 5 % Dextrose Normosol-M

[a] Number of participants with available outcome data included in the analysis, with the number of participants randomized in parenthesis

[b] Number of participants with surgical/medical condition, with the percentage given in parenthesis

[c] Age is expressed as the mean± standard deviation (SD) or as the median with the interquartile range in parenthesis

[d] D5NR composition: Na 140 meq/L, Cl 98 meq/L, K 5 meq/L, acetate 27 meq/L

[e] D5NM composition: Na 40 meq/L, Cl 40 meq/L, K 13 meq/L, acetate 16 meq/L

Table 2 Risk of bias summary

First author/year of study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Brazel/1996 [17]	Unclear	Unclear	High risk	Low risk	Low risk	Low risk
Montanana/2008 [18]	Low risk	Unclear	High risk	Low risk	Low risk	Low risk
Ang/2008 [24]	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Yung/2009 [22]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Kannan/2010 [19]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
Neville/2010 [15]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
Choong/2011 [14]	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
Rey/2011 [23]	Low risk	Unclear	Unclear	Low risk	High risk	Low risk
Saba/2011 [21]	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
Coulthard/2012 [16]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
Baron/2013 [20]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

cut-off value, and these were the values used in the meta-analysis.

There were seven RCTs which reported on mean pNa levels after maintenance IVF therapy, the duration of which varied across studies, ranging from approximately 12 to 48 h. Pooled estimates showed that mean pNa levels in children who received hypotonic fluids were significantly lower than those who received isotonic fluids (7 studies, 378 participants, MD −1.75, 95 % CI −2.37 to −1.14) (see Fig. 4). In addition, the absolute change in pNa levels from baseline was also significantly greater in children who received hypotonic fluids than in those who received isotonic fluids (3 studies, 211 participants MD −2.09 mmol/L, 95 % CI −2.85 to −1.34) (see Fig. 5). Among these latter three RCTs, two reported decreased pNa level with the use of either hypotonic or isotonic fluids [15, 23], while the third reported an increase in pNa level compared to baseline [21]. The study of Brazel et al. [17] was not included in the analysis for mean pNa level and change in pNa level because these data were not available in the published article and we were unable to retrieve them from the authors.

In addition to the protective effect of isotonic fluids in reducing the risk for hyponatremia, isotonic fluids also did not significantly increase the risk for developing hypernatremia compared to hypotonic fluids (7 studies, 790 participants, RR 0.83, 95 % CI 0.41–1.67). In exception to all of the other RCTs, Kannan et al. defined hypernatremia as pNa>150 mmol/L [19]. When the study by Kannan et al. was not included in the analysis, the results remained the same (6

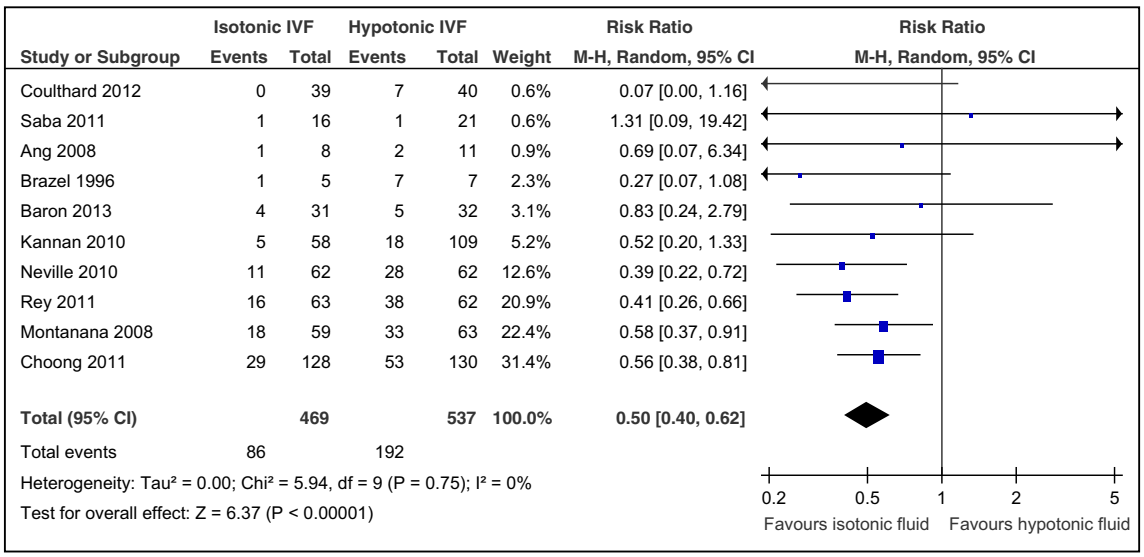

Fig. 2 Risk of developing hyponatremia with isotonic versus hypotonic maintenance intravenous fluid (*IVF*) therapy in hospitalized children. *Events* Number of subjects who developed hyponatremia during study period, *Total* number of participants, *CI* confidence interval

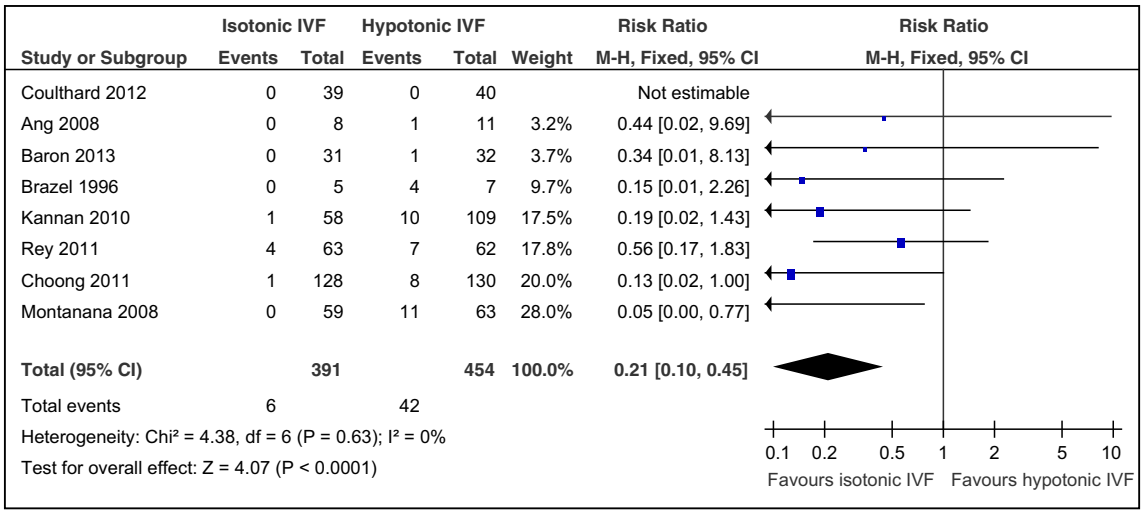

Fig. 3 Risk of developing severe hyponatremia with isotonic versus hypotonic maintenance IVF therapy in hospitalized children. *Events* Number of subjects who developed severe hyponatremia [plasma sodium level (pNa)<130 mmol/L], *Total* number of participants

studies, 623 participants, RR 0.88, 95 % CI 0.40–1.94) (see Fig. 6).

Patient-centered outcomes

There was no report of mortality directly attributed to dysnatremia. Of the 11 RCTs, two reported the occurrence of death among their study population [19, 20]. Kannan et al. [19] reported that one of their subjects died of acute respiratory distress syndrome. This child had been randomized to the isotonic group, and his pNa was normal throughout the study period [19]. Baron et al. reported the death of three of their patients, all of whom were randomized to receive hypotonic IVF. The pNa level of these patients remained ≥130 mmol/L throughout the study, and the cause(s) of death was determined not to be related to the maintenance IVF therapy [20].

Kannan et al. [19] reported one case of hyponatremic encephalopathy in a child diagnosed with acute intermittent porphyria. This child was randomized to receive 0.18 % saline in 5 % dextrose at a two-thirds maintenance rate. He had baseline hyponatremia (pNa = 132 mmol/L) which then decreased to 126 and 124 mmol/L at 12 and 48 h following the initiation of IVF, respectively. He manifested with seizures and stupor, but eventually improved after correction with 3 % saline [19].

Two studies reported the occurrence of hypertension among their participants [14, 18]. Analysis showed that the risk for developing hypertension was not significantly increased with the use of isotonic solution in maintenance IVF therapy (2 studies, 380 participants, RR=0.91, 95 % CI 0.40–2.06) (Forrest plot not shown).

Other outcomes of interest, such as the development of hyperchloremic metabolic acidosis and other manifestations of volume overload (e.g., congestive heart failure, pulmonary edema), were not reported in any of the 11 studies included in this systematic review.

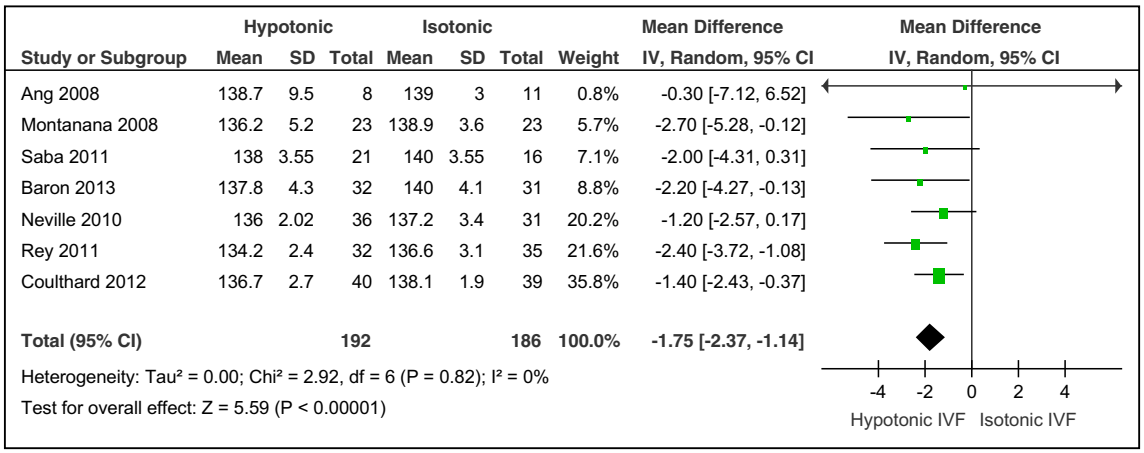

Fig. 4 Mean pNa following isotonic versus hypotonic maintenance IVF therapy in hospitalized children. *Mean* Mean pNa level, *SD* standard deviation, *Total* number of participants

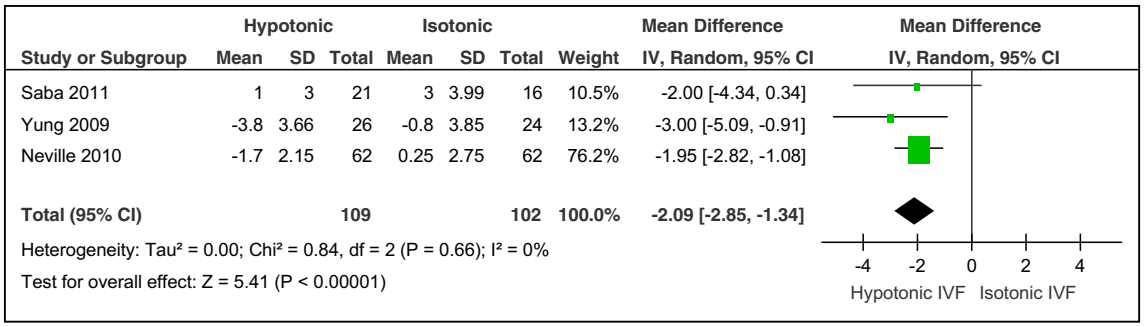

Fig. 5 Change in pNa following isotonic versus hypotonic maintenance IVF therapy in hospitalized children. *Mean* Mean change in pNa, *Total* number of participants

Subgroup analysis

Three RCTs determined the effect of fluid volume on the risk of hyponatremia [19, 15, 16]. However, the pooled data were limited and heterogeneous and, hence, insufficient to provide any clear information on the effect of restricting fluid volume. Subgroup analysis with regards to a child's condition, whether surgical or medical, was not done because of insufficient information available (i.e., results were not reported separately in studies which enrolled both surgical and non-surgical patients and we were unable to obtain this data from the authors). Lastly, there were no RCTs which reported on the effect of age; hence, subgroup analysis with regards to age was not carried out.

Discussion

The administration of maintenance IVF is a basic component of the care provided to hospitalized children. However, recent evidence does not appear to support the traditional practice of prescribing hypotonic IVF [25]. Since 2006, there have been at least six published systematic reviews which have addressed the issue of appropriate maintenance IVF tonicity among hospitalized children [2, 7–11], half of which included a meta-analysis [7, 10, 11]. Earlier reviews cautioned that the use of hypotonic IVF as maintenance fluid is potentially dangerous, but due to the paucity of well-designed prospective trials, the authors of these reviews were not able to determine with certainty which fluid regimen is safer and more effective [7, 8].

However, several RCTs published subsequently to these earlier reviews have enabled the authors of more recent reviews to conclude that the traditional practice of prescribing hypotonic IVF to hospitalized children is indeed associated with the development of hospital-acquired hyponatremia and, consequently, that its routine use must be reconsidered. These authors also concluded that isotonic IVF appears to be the safer choice in terms of the risk for developing hyponatremia [2, 9–11].

The first meta-analysis on the subject was carried out by Choong et al. in 2006 in which they pooled two RCTs, one cohort study, and one retrospective chart review [7]. Their analysis showed that the use of hypotonic IVF significantly

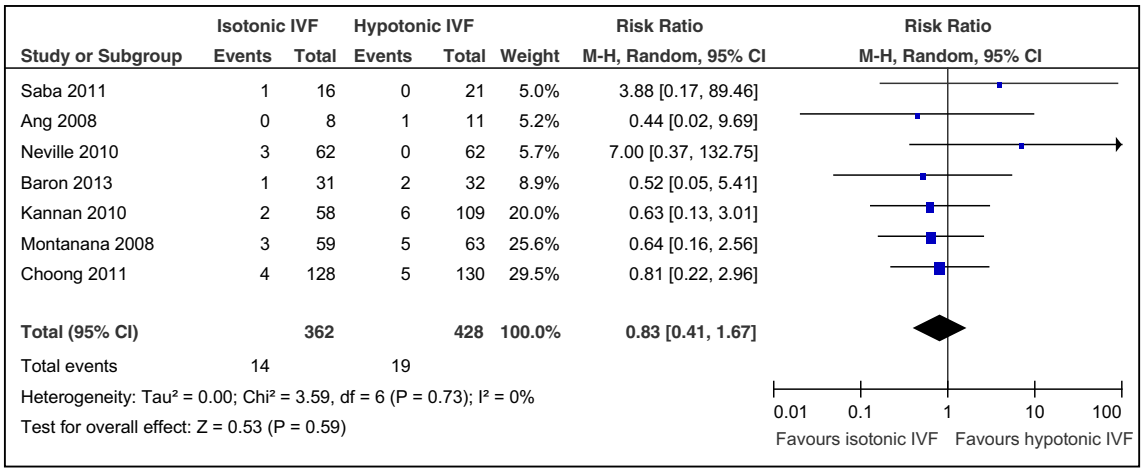

Fig. 6 Risk of developing hypernatremia with isotonic versus hypotonic maintenance IVF therapy. *Events* Number of subjects who developed hypernatremia during the study period (pNa>145 mmol/L), *Total* number of participants

increased the risk of developing hyponatremia—by 17-fold—compared to isotonic fluids (OR 17.22, 95 % CI 8.67–34.2).

Wang et al. pooled eight RCTs (treated as 10 separate RCTs in their analysis) and also showed that there is a significantly higher risk for developing hyponatremia with the use of hypotonic IVF as compared to isotonic IVF (RR 2.24, 95 % CI 1.52–3.31) [10]. Foster et al. found similar results in their meta-analysis of ten RCTs (RR 2.37, 95 % CI 1.72–3.26) [11]. Furthermore, their subgroup analysis of hypotonic fluids with half-normal saline showed a comparable RR of 2.42 (95 % CI 0.32–4.45).

The findings of our systematic review are consistent with the results of the above-mentioned meta-analyses, and we therefore support their recommendation that the traditional practice of prescribing hypotonic maintenance IVF therapy to hospitalized children be seriously reconsidered. The higher computed odds ratio in the review by Choong et al. [7] may be partly explained by their inclusion of two non-RCTs and an RCT which enrolled patients who received fluid replacement therapy for acute gastroenteritis. In addition, the majority of the studies included in our meta-analysis, as well as in those of Wang et al. [10] and Foster et al. [11], excluded patients who had baseline hyponatremia [14, 18, 19, 21, 23], which may have reduced overestimation of the incidence of hyponatremia and, in turn, reduced the computed relative risk for developing hospital-acquired hyponatremia.

Our analysis also showed statistically significant lower pNa levels (MD −1.75 mmol/L, 95 % CI −2.37 to −1.14) and a greater drop in pNa from baseline (MD −2.09 mmol/L, 95 % CI −2.85 to −1.34) in children who received hypotonic fluids. Although the pooled mean difference in pNa level was statistically significant, it may not be clinically significant since the mean pNa levels in both isotonic and hypotonic groups were all within normal levels (i.e., pNa>135 mmol/L), except in the study by Rey et al. [23] (see Fig. 4). One explanation may be that the studies had a small sample size and were not actually designed to detect clinically significant differences. Also, in contrast to the usual clinical setting, pNa levels were monitored very closely in the RCTs, hence decreases in pNa levels were detected early and managed accordingly.

Compared to the meta-analyses by Choong et al. [7] and Foster et al. [11], two RCTs were not included in our review either because the intervention involved intra-operative fluid replacement therapy using the method proposed by Berry [26], or the population involved patients with acute gastroenteritis, the management of which includes fluid deficit therapy [27]. We included all of the RCTs included in the meta-analysis by Wang et al. [10].

The observed protective effect of isotonic fluids may be explained by the lower electrolyte-free water (EFW) content in such solutions. In the presence of increased levels of ADH, EFW excretion is impaired, which then results in a net positive balance in EFW and, consequently, dilutional hyponatremia [14]. It is well-documented that many of the conditions for which a child may be hospitalized are related to increased ADH levels due to the presence of factors such as pain, anxiety, post-operative state, nausea, vomiting, fever, sepsis, reduced circulating volume, respiratory disorders, central nervous system infections, and metabolic and endocrine disorders. Hence, each hospitalized child is virtually at risk for developing hyponatremia, and this risk becomes even greater with the use of hypotonic IVF [28].

The concern that isotonic fluids may increase the risk of hypernatremia was not evident in our study (RR 0.86, 95 % CI 0.41–1.82), which is consistent with the findings of earlier meta-analyses [7, 10, 11]. In addition, our analysis showed that the risk for hypertension, theoretically secondary to increased intravascular volume, was not significantly increased by the use of isotonic solutions.

A number of experts assert that the use of isotonic fluids for maintenance IVF therapy imposes an unnecessary intravenous sodium load that substantially increases when administration goes beyond 24 h [29, 30]. It has also been proposed that it is actually the administration of excessive volume of IVF that underlies the increased risk of hyponatremia in patients receiving maintenance IVF therapy—rather than the solution's tonicity. The phenomenon was described by Steele et al. [31], who noted a fall in pNa level in adult surgical patients despite the administration of near-isotonic IVF (Ringer's lactate). "Desalination" was also observed in a prospective cohort study wherein patients who became hyponatremic had a higher urine Na loss, a more negative Na balance, and greater diuresis than patients who remained isonatremic [32]. This phenomenon is not completely understood, but may be related to overexpansion of the extracellular fluid compartment from the saline infused during surgery in combination with increased ADH, natriuretic peptide and glomerular filtration rate, and suppression of aldosterone. The total effect is the excretion of a hypertonic urine and, ultimately, hyponatremia [12, 32, 33]. The aim of three of the RCTs included in our systematic review was to compare the risk of developing hyponatremia between those who received full maintenance fluid requirements and those who were given restricted fluid volume (½ to 2/3 the maintenance requirements) [15, 16, 19]. However, the pooled data were insufficient and heterogeneous, precluding any recommendation regarding the added value of restricting fluid volume. There is therefore a need for larger RCTs to further elucidate this matter.

The strength of this systematic review lies in the comprehensive search strategy and pre-specified inclusion criteria unbiased by a priori knowledge of the primary studies. The 11 studies included were all RCTs, albeit with some degree of variability in their methodology. Different intravenous fluids were compared, more so in the hypotonic group (Na content ranged from 20 to 100 mmol/L, but most studies used 0.45 %

NaCl in the hypotonic arm). In addition, time points and frequency of sampling for pNa levels differed across studies. In order to address the inherent heterogeneity in pooling data from different but relevant studies, we used the random effects method in our analysis.

This systematic review has a number of limitations. The RCTs included in the systematic review were all published papers, except for one RCT which only had its abstract published [24]. Thus, publication bias cannot be totally excluded. In addition, our predefined subgroup analyses were not presented in this review because data from individual studies were lacking and we were not able to request these from the respective authors. Lastly, interpretation of risks associated with the use of hypotonic and isotonic IVF pertain only to the first 48 h of maintenance IVF therapy. Hence, our results may not be applicable to patients receiving maintenance IVF for longer duration.

Conclusion

The standard practice of using hypotonic fluids significantly increases the risk of developing hyponatremia, while the use of isotonic IVF does not increase the risk of hypernatremia, volume overload, or hypertension. Hence, it would appear that the isotonic saline solution is the safer empiric maintenance IVF for use in the general pediatric population. The practice of prescribing hypotonic saline solutions for maintenance IVF among hospitalized children is not supported by currently available evidence and must, therefore, be seriously reconsidered.

Acknowledgments We would like to thank Prof. Cynthia P. Cordero (Department of Clinical Epidemiology, College of Medicine, University of the Philippines Manila), for her assistance in doing the meta-analysis.

References

1. Moritz ML, Ayus JC (2011) Intravenous fluid management for the acutely ill child. Curr Opin Pediatr 23:186–193
2. Easley D, Tillman E (2013) Hospital-acquired hyponatremia in pediatric patients: a review of the literature. J Pediatr Pharmacol Ther 18:105–111
3. Moritz ML, Ayus JC (2005) Preventing neurological complications from dysnatremias in children. Pediatr Nephrol 20:1687–1700
4. Holliday MA, Segar WE (1957) The maintenance need for water in parenteral fluid therapy. Pediatrics 19:823–832
5. Moritz ML, Ayus JC (2007) Hospital-acquired hyponatremia—why are hypotonic parenteral fluids still being used? Nat Clin Pract Nephrol 3:374–382
6. Freeman MA, Ayus JC, Moritz ML (2012) Maintenance intravenous fluid prescribing practices among pediatric residents. Acta Paediatr 101:465–468
7. Choong K, Kho EM, Menon K, Bohn D (2006) Hypotonic versus isotonic saline in hospitalised children: a systematic review. Arch Dis Child 91:828–835
8. Beck CE (2007) Hypotonic versus isotonic maintenance intravenous fluid therapy in hospitalized children: a systematic review. Clin Pediatr 46:764–770
9. Alves JTL, Troster EJ, de Oliveira CAC (2011) Isotonic saline solution as maintenance intravenous fluid therapy to prevent acquired hyponatremia in hospitalized children. J Pediatr (Rio J) 87:478–486
10. Wang J, Xu E, Xiao Y (2014) Isotonic versus hypotonic maintenance IV fluids in hospitalized children: a meta-analysis. Pediatrics 133: 105–113
11. Foster BA, Tom D, Hill V (2014) Hypotonic versus isotonic fluids in hospitalized children: a systematic review and meta-analysis. J Pediatr 165:163–169
12. Choong K, Bohn D (2007) Maintenance parenteral fluids in the critically ill child. J Pediatr (Rio J) 83:S3–S10
13. Higgins J, Green S, eds (2011) Cochrane handbook for systematic reviews of interventions version 5.1.0. Available at: www.cochrane-handbook.org. Accessed March 2013
14. Choong K, Arora S, Cheng J, Farrokhyar F, Reddy D, Thabane L, Walton JM (2011) Hypotonic versus isotonic maintenance fluids after surgery for children: a randomized controlled trial. Pediatrics 128: 857–866
15. Neville KA, Sanderman DJ, Rubinstein A, Henry GM, McGlynn M, Walker JL (2010) Prevention of hyponatremia during maintenance intravenous fluid administration: a prospective randomized study of fluid type versus fluid rate. J Pediatr 156:313–319
16. Coulthard MG, Long DA, Ullman AJ, Ware RS (2012) A randomised controlled trial of Hartmann's solution versus half normal saline in postoperative paediatric spinal instrumentation and craniotomy patients. Arch Dis Child 97:491–496
17. Brazel PW, McPhee IB (1996) Inappropriate secretion of antidiuretic hormone in postoperative scoliosis patients: the role of fluid management. Spine 21:724–727
18. Montañana PA, Alapont M, Ocon AP, Lopez PO, Prats JL, Parreño JT (2008) The use of isotonic fluid as maintenance therapy prevents iatrogenic hyponatremia in pediatrics: A randomized, controlled open study. Pediatr Crit Care Med 9:589–597
19. Kannan L, Lodha R, Vivekanandhan S, Bagga A, Kabra S, Kabra M (2010) Intravenous fluid regimen and hyponatremia among children: a randomized controlled trial. Pediatr Nephrol 25:2303–2309
20. Baron FA, Meregalli CN, Rombola VA, Bolasell C, Pigliapoco VE, Bartoletti SE, Debaisi GE (2013) Hypotonic versus isotonic intravenous maintenance fluids in critically ill pediatric patients: a randomized clinical trial. Arch Argent Pediatr 111:281–287
21. Saba TG, Fairbairn J, Houghton F, Laforte D, Foster BJ (2011) A randomized controlled trial of isotonic versus hypotonic maintenance intravenous fluids in hospitalized children. BMC Pediatr 11:82
22. Yung M, Keeley S (2009) Randomised controlled trial of intravenous maintenance fluids. J Paediatr Child Health 45:9–14
23. Rey C, Los-Arcos M, Hernandez A, Sanchez A, Diaz J, Lopez-Herce J (2011) Hypotonic versus isotonic maintenance fluids in critically ill children: a multicenter prospective randomized study. Acta Paediatr 100:1138–1143
24. Ang VD, Anacleto FE, Mantaring JB (2010) Effect of isotonic versus hypotonic parenteral fluids on the serum sodium levels of children admitted to a tertiary hospital: An open, randomized, controlled trial (A preliminary study). Pediatr Nephrol 25:9
25. Roberts KB (2001) Fluid and electrolytes: parenteral fluid therapy. Pediatr Rev 22:380–387
26. Dagli G, Orhan ME, Kurt E (1997) The effects of different hydration fluids used in pediatric anesthesia on blood glucose, electrolytes, and cardiovascular stability. GATA Bulteni 39:146–152
27. Neville KA, Verge CF, Rosenberg AR, O'Meara MW, Walker JL (2006) Isotonic is better than hypotonic saline for intravenous

rehydration of children with gastroenteritis: a prospective randomised study. Arch Dis Child 91:226–232
28. Moritz ML, Ayus JC (2010) New aspects in the pathogenesis, prevention and treatment of hyponatremic encephalopathy in children. Pediatr Nephrol 25:1225–1238
29. Holliday MA (2005) Isotonic saline expands extracellular fluid and is inappropriate for maintenance therapy. Pediatrics 115:93
30. Hatherhill M (2014) Rubbing salt in the wound: the case against isotonic parenteral maintenance solution. Arch Dis Child 89:414–418
31. Steele A, Gowrishankar M, Abrahamson S, Mazer CD, Feldman RD, Halperin ML (1997) Postoperative hyponatremia despite near isotonic saline infusion: a phenomenon of desalination. Ann Intern Med 126:20–25
32. Eulmesekian PG, Perez A, Minces PG, Bohn D (2010) Hospital-acquired hyponatremia in postoperative pediatric patients: prospective observational study. Pediatr Crit Care Med 11:479–483
33. Taylor D, Durward A (2004) Pouring salt on troubled waters. Arch Dis Child 89:411–414