Isotonic Versus Hypotonic Maintenance IV Fluids in Hospitalized Children: A Meta-Analysis

meta-analyses require very little capital - just access to articles. Xian seems to be pretty remote although it is one of the powerhouse universities of China.

landmark in Xian pagoda houses Buddhist manuscripts

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KEY WORDS

intravenous fluid, hypotonic fluid, isotonic fluid, hyponatremia, children

ABBREVIATIONS

ADH—antidiuretic hormone
CI—confidence interval
IV—intravenous
pNa—plasma sodium
PRISMA—Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT—randomized controlled trial
RR—relative risk

Dr Wang designed the study, searched databases, selected studies, extracted raw data, assessed risk of bias, carried out the analysis, and drafted the manuscript; Dr Xu helped with raw data extraction, independently assessed risk of bias, helped with analysis, and critically reviewed the manuscript; Dr Xiao designed the study, independently selected studies, helped with analysis, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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they did this in <6 months; check the abstract to see how you can know

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abstract

OBJECTIVE: To assess evidence from randomized controlled trials (RCTs) on the safety of isotonic versus hypotonic intravenous (IV) maintenance fluids in hospitalized children.

METHODS: We searched PubMed, Embase, Cochrane Library, and clinicaltrials.gov (up to April 11, 2013) for RCTs that compared isotonic to hypotonic maintenance IV fluid therapy in hospitalized children. Relative risk (RR), weighted mean differences, and 95% confidence intervals (CIs) were calculated based on the effects on plasma sodium (pNa). The risk of developing hyponatremia (pNa <136 mmol/L), severe hyponatremia (pNa <130 mmol/L), and hypernatremia (pNa >145 mmol/L) was evaluated. We adopted a random-effects model in all meta-analyses. Sensitivity analyses by missing data were also performed.

RESULTS: Ten RCTs were included in this review. The meta-analysis showed significantly higher risk of hypotonic IV fluids for developing hyponatremia (RR 2.24, 95% CI 1.52 to 3.31) and severe hyponatremia (RR 5.29, 95% CI 1.74 to 16.06). There was a significantly greater fall in pNa in children who received hypotonic IV fluids (–3.49 mmol/L versus isotonic IV fluids, 95% CI –5.63 to –1.35). No significant difference was found between the 2 interventions in the risk of hypernatremia (RR 0.73, 95% CI 0.22 to 2.48). None of the findings was sensitive to imputation of missing data.

CONCLUSIONS: Isotonic fluids are safer than hypotonic fluids in hospitalized children requiring maintenance IV fluid therapy in terms of pNa. *Pediatrics* 2014;133:105–113

Background in a nutshell

Almost EVERY child admitted to the hospital in this day and age has a known trigger for SIADH (it's not just oat-cell tumors, you know). Known causes are - respiratory infection, respiratory disease, post-op pain, post-op nausea, medications (vincristine, SSRIs, morphine, cipro, and others), CNS disease (meningitis, shunt malfunction.

The Holliday-Segar formula was designed in an age when SIADH wasn't so common.

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Maintenance intravenous (IV) fluids are designed to maintain homeostasis when a patient is unable to uptake required water, electrolytes, and energy. After Holliday and Segar made recommendations for maintenance fluid in children,[1] hypotonic fluids are still the most commonly prescribed IV fluids for pediatric hospitalized patients.[2–4] Their hypotonic formula was based on the energy expenditure of healthy children and the composition of human breast and cow milk.[1] Hypotonic fluids according to their recommendations may be appropriate for healthy children. Nevertheless, they may not be suitable for all hospitalized children.[5,6]

Hyponatremia, defined as a plasma sodium (pNa) level of <136 mmol/L,[7] draws excess water into cells and causes them to swell. It mainly manifests as central nervous system symptoms such as lethargy, irritability, muscle weakness, seizures, and coma, or even death in the most severe cases.[8] Hospitalized children are often in a stressed state and easily secrete excess antidiuretic hormone (ADH), which stimulates water retention.[9] In this setting, children are prone to develop hyponatremia, especially when receiving hypotonic fluids.[9]

Accumulating clinical evidence suggests that Holliday and Segar's recommendations are inappropriate for most hospitalized children.[10–20] Clinical evidence suggests that the routine use of hypotonic fluids contributes to the development of iatrogenic hyponatremia, whereas isotonic fluids offer effective prophylaxis against it.[10–20] However, traditional guidelines and textbooks continue recommending hypotonic maintenance fluids for pediatric patients.[21] Early systematic reviews have evaluated isotonic versus hypotonic maintenance IV fluids in hospitalized children,[6,22–24] but only included limited randomized controlled trials (RCTs). Here, we added more recent RCTs to perform an updated systematic review and meta-analysis to address this issue.

standardized checklist

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting of this meta-analysis.[25]

did they exclude any database? There is a psych/behav sci database that they neglected but not so importantf or this topic

Search Strategy

We searched PubMed, Embase, Cochrane Controlled Clinical Trials Register, and ClinicalTrials.gov (up to April 11, 2013) for potentially relevant publications without any language restriction. We modified the search strategy from a previous systematic review.[6] The detailed search strategy is presented in the Supplemental Information. We also screened references of previous systematic reviews and identified relevant articles.

take the advanced PubMed course to learn this.

Study Selection

Two authors independently screened the titles and abstracts of potentially relevant citations. They then read the full texts of citations needing additional evaluation. Discrepancies were resolved through group discussion. The inclusion criteria were as follows:[1] studies on RCTs,[2] studies on hospitalized children aged from 1 month to 17 years,[3] and studies comparing isotonic and hypotonic maintenance IV fluid therapy. Solutions were classified as isotonic if they had the same or near osmotic pressure as blood (eg, 0.9% saline, Hartmann's solution, or Ringer's solution) or hypotonic if they had a lower osmotic pressure than blood (eg, 0.45% saline, 0.3% saline, or 0.18% saline). Exclusion criteria were[1] non-RCT studies,[2] letters and case reports,[3] studies published as abstracts only,[4] studies involving neonates,[5] studies of fluid resuscitation or rehydration,[6] and patients with preexisting hyponatremia or comorbidities that resulted in sodium disturbance (eg, renal diseases, liver cirrhosis, congestive heart failure, and diuretic therapies).

Data Extraction

A standard reporting form developed by PRISMA[25] was used to extract data. One author extracted data, and another checked all forms. We extracted the following information: methods of the study (as per assessment of risk of bias), characteristics of study population (number, age, and diagnosis), description of the interventions and comparisons, and outcomes. The primary outcome was hyponatremia (pNa <136 mmol/L). Secondary outcomes were severe or symptomatic hyponatremia (pNa <130 mmol/L), pNa and pNa changes after IV fluid therapy, hypernatremia (pNa >145 mmol/L), and adverse events attributable to IV fluid administration and/or pNa derangements (death, cerebral edema, seizures, hypertension, and length of stay).

Do you agree with the definitions?

How many secondary outcomes are listed here?

How many are categorical (yes/no) and how many are continuous data?

Assessment of Risk of Bias

We addressed the methodologic quality of included studies using the Cochrane risk-of-bias tool, which includes domains for sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias.[26] Discrepancies were resolved through group discussion.

aka
1. how they randomized
2. blinding
3. missing data
4. intention to treat
5. pub bias etc.

here's that 'group' again.

Analysis

really?? read on.

If >1 study reported the same outcome, statistical pooling was adopted to estimate the intervention effects. For dichotomous outcomes, we used relative risk (RR) and 95% confidence intervals (CIs). For continuous outcomes, we used weighted mean differences and 95% CIs. All pooled estimates of the intervention effects

this would have been sacrilege for most of the 20th Century...

American researchers often neglect non-English studies...

usually a third is a tie-breaker...

2 RCTs have been completed since then. 1 published

Hartmann vs Ringer: one invented by a Brit, the other an American; one an internist the other a pediatrician; one has Na 131, the other 130; one we still use in modern care - and it's not Ringer's but 'lactated Ringer's' which is Hartmann's.

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they repeated the analysis multiple ways, just so the accuracy of their assumptions could be tested.

since meta-analyses are all about combining study results, you want to make sure you're combining apples w/ apples (aka they are homogenous) So you'd want a test for 'heterogeneity' to be non-significant

were calculated under a random-effects model.[27] First, we performed analysis of available cases in which data were analyzed for every participant for whom the outcome was obtained. We then performed a sensitivity analysis in which dichotomous data were analyzed according to the intention-to-treat principle, and continuous data were analyzed by assuming a fixed difference between the actual mean for the missing data.[26] Heterogeneity was determined by using the I^2 statistic and I^2 value of 0% to 25%, 26% to 49%, 50% to 74%, and 75% to 100% were assigned unimportant, low, moderate, and high heterogeneity, respectively.[28] All statistical analyses were done with RevMan 5.1 (the Cochrane Collaboration, Copenhagen, Denmark).

Pasman repeated the analysis after adding in the new Argentine study using Revman. Took him 15 minutes.

RESULTS

Study Selection

Figure 1 shows the process of study selection. We identified 10 studies comparing isotonic and hypotonic maintenance IV fluid therapy in hospitalized children according to our criteria.[10–16,20,29,30] Two were unpublished studies, and we failed to access their data by contacting the authors.[29,30] Two studies were considered as 4 RCTs because they compared hypotonic and isotonic fluids at 2 maintenance rates.[10,13] Therefore, 10 RCTs were included in this review.

Bonus

Study Characteristics

Table 1 shows characteristics of the included RCTs. Five RCTs exclusively enrolled children undergoing surgery,[13,15,16,20] 1 RCT exclusively enrolled children with illnesses that required nonsurgical treatment,[14] and 4 RCTs enrolled both types of patients.[10–12] The shortest follow-up ranged from 8 to 72 hours. mostly post-op surgical

Risk of Bias

Table 2 shows the risk of bias for each study. Although all studies were reported as RCTs, 3 lacked adequate description in sequence generation[13,20] and 2 in allocation concealment.[12,20] Four studies used blinding methods for participants, caregivers, and researchers,[10,11,15] 5 studies did not use blinding methods[12–14,20] and 1 study reported contradictory data in its abstract and text.[16] One study had a high risk of incomplete outcome data because of a relatively large number of losses during follow-up.[11] Two studies were classified as high risk in the domain of free of selective reporting because they did not report the primary outcome hyponatremia.[10] Four studies were classified as "unclear" because their protocols were unavailable, which made it difficult to make a judgment.[12,13,20] Three studies also enrolled participants with preexisting hyponatremia, which may introduce bias in our analysis.[12,13] One of them supplied separate data for participants of interest for our analysis.[12] The other 2 studies did not supply these data, but their raw data were directly extracted for our analysis considering a small proportion of participants with preexisting hyponatremia.[13]

more common than u think.

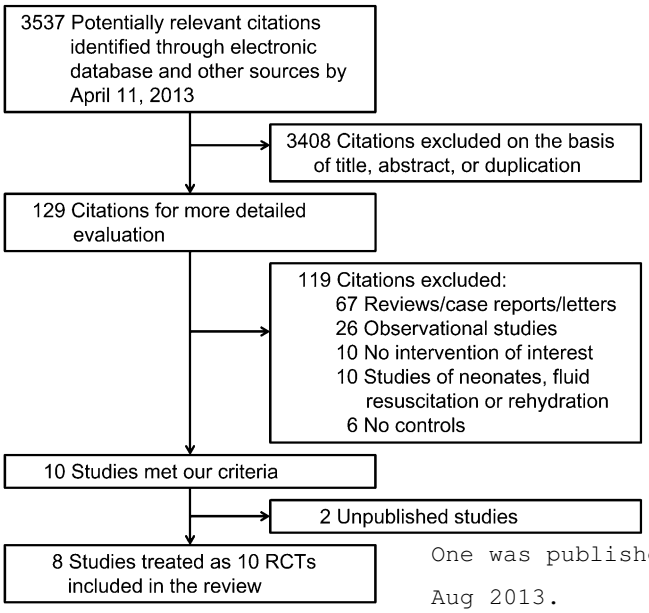
wasn't this an exclusion criterion?

those authors kind enough to give actual data

pNa

All extracted data are presented in Table 3 for meta-analysis of pNa outcomes. Because the study by Kannan et al defined hyponatremia as pNa <130 mmol/L,[14] it was initially excluded in the pooled analysis of hyponatremia. The analysis showed that hypotonic IV fluids significantly increased the risk of hyponatremia (RR 2.24, 95% CI 1.52 to 3.31, $P < .0001$, I^2 = 14%; Fig 2). When the study by Kannan et al was included,[14] the result was similar (RR 2.30, 95% CI 1.58 to 3.37, $P < .0001$, I^2 = 12%). In 2 studies, no severe hyponatremia developed in either the isotonic or hypotonic arms.[11,16] Pooled analysis of other studies with available data showed that hypotonic IV maintenance fluids also significantly increased the risk of severe hyponatremia (RR 5.29, 95% CI 1.74 to 16.06, $P = .003$, I^2 = 0%; Fig 3). Mean pNa in children after hypotonic IV fluids was

when you design a study, use accepted defin-itions from the lit



One was published in Aug 2013.

FIGURE 1
Flow diagram of study selection.

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looks like apples and oranges. dropping 2 points in 8 hrs is way different than dropping 2 points in 72 hrs

TABLE 1 Characteristics of Included RCTs of Hypotonic Versus Isotonic Maintenance IV Fluid Therapy in Hospitalized Children

Study	Condition	Follow-up, h	Hypotonic			Isotonic		
			N[a]	Age,[b] y	Solution	N[a]	Age,[b] y	Solution
Brazel 1996	Surgical	≥72	7	Adolescent	0.3% S and 3% D; 0.18% S and 4% D	5	Adolescent	Hartman's solution
Yung 2009a	Surgical and medical	≥12	15	4.7 (1.4–8.9)	0.18% S and 4% D	13	5.3 (0.9–12)	0.9% S
Yung 2009b	Surgical and medical	≥12	11	3.7 (1.5–14.7)	0.18% S and 4% D	11	15.4 (10.8–15.9)	0.9% S
Kannan 2010	Medical	≥24	56	4.0 (1.1–6.0)	0.18% S and 5% D at full rate	58	3.0 (1.0–7.0)	0.9% S and 5% D at full rate
	align	≥24	53	3.0 (0.8–5.5)	0.18% S and 5% D at 2/3 rate			
Neville 2010a	Surgical	≥8	31[c]	9.9 (2.0–15.0)	0.45% S and 5% D at half rate	31[c]	9.4 (1.0–14.9)	0.9% S and 5% D at half rate
Neville 2010b	Surgical	≥8	31	9.1 (0.9–14.9)	0.45% S and 2.5% D at full rate	31[c]	8.4 (0.6–14.9)	0.9% S and 2.5% D at full rate
Choong 2011	Surgical	≥24	130	9.2 ± 5.7	0.45% S and 5% D	128	9.2 ± 5.5	0.9% S and 5% D
Rey 2011	Surgical and medical	≥12	62[d]	4.7 (1.7–9.9)	30–50 mmol/L NaCl and 20 mmol/L KCl	63[e]	4.9 (2.0–10.6)	136 mmol/L NaCl and 20 mmol/L KCl
Saba 2011	Surgical and medical	≥8	21	8.9 (1.7–16.5)	0.45% S and 5% D	16	8.2 (2.8–14.3)	0.9% S and 5% D
Coulthard 2012	Surgical	≥16	41	11.5 (6.0–14.1)	0.45% S and 5% D	41	11.3 (4.3–13.9)	Hartmann's and 5% D

what the heck is this? maybe a secret code to Chinese in the US?

D, dextrose; KCl, potassium chloride; NaCl, sodium chloride; S, saline.
[a] Number of participants reported in the tables of baseline characteristics.
[b] Age is expressed as median (interquartile range), median (range), or mean ± SD.
[c] Including 2 participants with preexisting hyponatremia.
[d] Including 23 participants with preexisting hyponatremia.
[e] Including 18 participants with preexisting hyponatremia.

Questions to answer about the 8 studies

1. How many used Hartmann's?
2. How many followed > 24 hrs?
3. How many kids had hyponatremia before getting that hypotonic solution?
4. From Table 2, what was the 'best' RCT included?
   (hint: remember the Jadad Score from the probiotic & asthma journal club?)

yes but is 2 meq/L really sig?

TABLE 2 Risk of Bias of Included Studies

Study	Adequate Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data Addressed	Free of Selective Reporting	Free of Other Bias	Comments
Brazel 1996	Unclear	Unclear	No	Yes	Unclear	Unclear	
Yung 2009a	Yes	Yes	Yes	Yes	No	Unclear	Hyponatremia was not reported
Yung 2009b	Yes	Yes	Yes	Yes	No	Unclear	Hyponatremia was not reported
Kannan 2010	Yes	Yes	No	Yes	Yes	Unclear	
Neville 2010a	Unclear	Yes	No	Yes	Unclear	No	Participants with preexisting hyponatremia (6%)
Neville 2010b	Unclear	Yes	No	Yes	Unclear	No	Participants with preexisting hyponatremia (0%–6%)
Choong 2011	Yes	Yes	Yes	Yes	Yes	Unclear	
Rey 2011	Yes	Unclear	No	Yes	Unclear	No	Participants with preexisting hyponatremia (29%–37%)
Saba 2011	Yes	Yes	Yes	No	Yes	Unclear	Postrandomization exclusions (19 of 59 subjects)
Coulthard 2012	Yes	Yes	Unclear	Yes	Yes	Unclear	

significantly lower than those who received isotonic IV fluids (−2.09 mmol/L, 95% CI −2.91 to −1.28, $P < .00001$, I^2 = 47%; Fig 4). Furthermore, the fall in pNa was also significantly greater in children who received hypotonic IV fluids (−3.49 mmol/L, 95% CI −5.63 to −1.35, $P = .001$, $I^2 = 87\%$; Fig 5). However, our analysis showed no significant difference between the 2 interventions in the risk of hypernatremia with or without inclusion of the study by Kannan et al,[14] which defined hypernatremia as pNa >150 mmol/L (without the study by Kannan et al: RR 0.73, 95% CI 0.22 to 2.48, $P = .62$, $I^2 = 0\%$; with the study by Kannan et al: RR 0.98, 95% CI 0.38 to 2.57, $P = .97$, $I^2 = 0\%$). Because the studies by Neville et al also enrolled a small proportion of participants with preexisting hyponatremia (0%–6%),[13] we excluded these subjects to see whether they would influence the results. We found that this population did not affect our findings (data not shown).

We also performed a sensitivity analysis to see whether missing data of included studies would influence our findings. For the risks of hyponatremia, severe hyponatremia, and hypernatremia, we extracted intention-to-treat data to perform sensitivity analysis. For pNa and changes in pNa after fluid treatment, we assumed that the missing data in the hypotonic fluid arm had averaged 1 mmol/L higher than the observed data itself, and the missing data in the isotonic fluid arm had

OK..but that's an assumption all right

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TABLE 3 Extracted Data From Included Studies for Meta-Analysis of Outcomes Relating to pNA Levels

Study	Hypotonic						Isotonic					
	N	pNa Changes	pNa End	Hypo	Severe Hypo	Hyper	*N*	pNa Changes	pNa End	Hypo	Severe Hypo	Hyper
Brazel 1996	7 (7)	−12.5 ± 2.8	129.0 ± 3.8	7	4	0	5 (5)	−2.0 ± 1.9	138.0 ± 6.5	1	0	0
Kannan 2010[a]	56 (56)	NA	NA	8	8	2	58 (58)	NA	NA	1	1	2
	53 (53)	NA	NA	2	2	4						
Yung 2009a	15	−3 ± 3.3	NA	NA	NA	NA	13 (15)	−0.2 ± 3.5	NA	NA	NA	NA
Yung 2009b	11 (12)	−4.9 ± 4.0	NA	NA	NA	NA	11 (12)	−1.5 ± 4.3	NA	NA	NA	NA
Neville 2010a[b]	31 (37)	−1.9 ± 2.0	136 ± 2.1	10	NA	0	31 (37)	−0.1 ± 3.2	138 ± 3.6	5	NA	2
Neville 2010b[b]	31 (37)	−1.5 ± 2.3	136 ± 2.1	9	NA	0	31 (37)	0.6 ± 2.2	138 ± 1.9	1	NA	0
Choong 2011	112 (130)	NA	NA	47	7	4	106 (128)	NA	NA	26	1	3
Rey 2011[c]	39 (43)	NA	134.5 ± 2.7	19	3	NA	45 (50)	NA	137.6 ± 3.2	8	1	NA
Saba 2011[d]	21 (32)	1.1 ± 3.0	138.1 ± 2.4	1	0	0	16 (27)	2.4 ± 3.1	139.4 ± 3.0	1	0	1
Coulthard 2012	40 (41)	NA	136.7 ± 2.7	7	0	0	39 (41)	NA	138.1 ± 1.9	0	0	0

Hyper, hypernatremia; Hypo, hyponatremia; *N*, number of participants expressed as available cases (randomized cases); NA, not available; pNa end, pNa after IV fluids; pNa changes, pNa changes after IV fluids.

[a] Hyponatremia defined as sodium <130 mmol/L; hypernatremia defined as >150 mmol/L.

[b] Data at 8 h.

[c] Data at 12 h for continuous outcomes, data throughout the study period for categorical outcomes. We assumed that all withdrawn cases were from those without preexisting hyponatremia.

[d] Data interpreted from figures.

Classic Forest Plot – the size of the square indicates the sample size

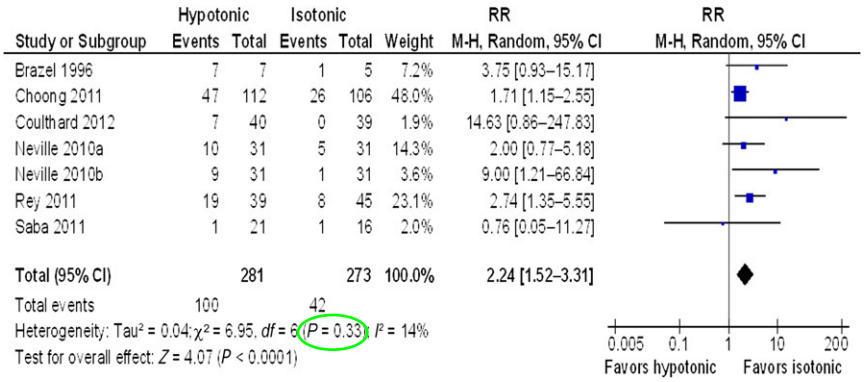

FIGURE 2 categorical (yes/no) so uses RR

Meta-analysis of data for the outcome of hyponatremia comparing hypotonic with isotonic IV maintenance fluids in hospitalized children.

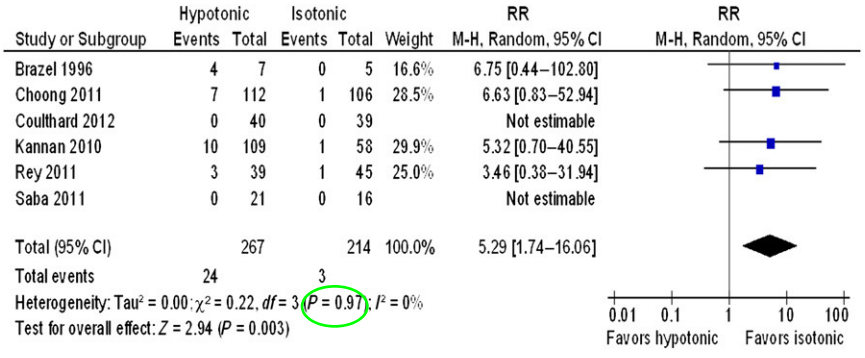

FIGURE 3 also uses RR (signif if it doesn't cross 1)

Meta-analysis of data for the outcome of severe hyponatremia comparing hypotonic with isotonic IV maintenance fluids in hospitalized children.

averaged 1 mmol/L lower than the observed data itself. The results were similar to those from the analysis of available cases (Table 4).

Heterogeneity was significant in the analysis of pNa and pNa changes with I^2 value of 47% and 87%, respectively. When the study by Brazel et al was excluded,[20] the I^2 value became 17% and 0, respectively, and the meta-analysis results remained nearly identical. No significant heterogeneity was present in the analyses of other outcomes.

Adverse Events

Adverse outcomes of interest were reported in 2 studies.[14,15] Kannan et al reported 1 death (1.72%, 1/58) in children receiving isotonic fluid for acute respiratory distress syndrome.[14] This child had normal pNa throughout the study period. They also reported 1 case of hyponatremic encephalopathy with seizures and stupor in children receiving hypotonic fluid.[14] Choong et al reported new-onset hypertension in 1.54% (2 of 130) children receiving hypotonic fluid and none in those receiving isotonic fluid.[15] The hospital length of stay was similar between the 2 types of fluids.[15]

Subgroup Analysis

Two of the included studies determined the effect of administration rate (full rate versus two-thirds rate, and full rate versus half rate) on pNa.[10,13] Their results showed that fluid type (isotonic or hypotonic solutions), not rate, determined the risk of hyponatremia and

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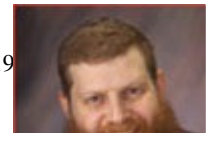

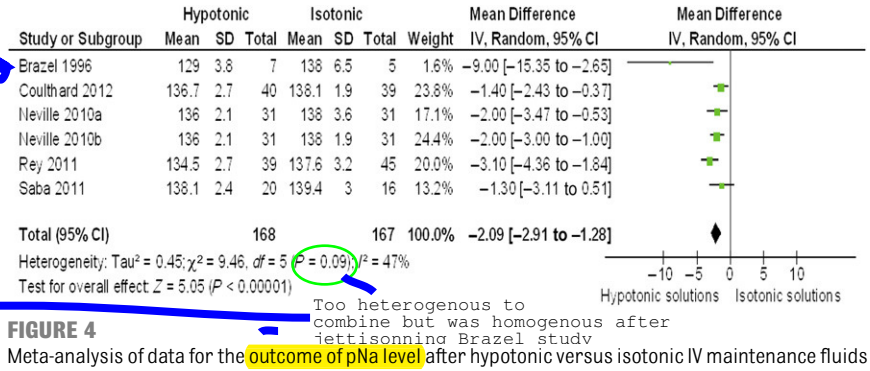

FIGURE 4

Meta-analysis of data for the outcome of pNa level after hypotonic versus isotonic IV maintenance fluids in hospitalized children.

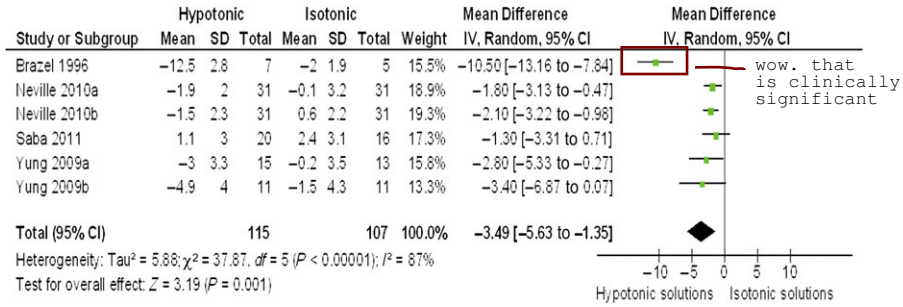

FIGURE 5

Meta-analysis of data for the outcome of change in pNa level after hypotonic versus isotonic IV maintenance fluids in hospitalized children.

TABLE 4 Sensitivity Analysis by Missing Data

Outcome	Data Source	No. of Studies	Hypotonic[a]	Isotonic[b]	RR or WMD	95% CI	*P*
Hyponatremia	ACA	7	281	273	2.24	1.52 to 3.31	<.0001
	ITT	7	327	325	2.23	1.57 to 3.18	<.00001
Severe hyponatremia	ACA	4	267	214	5.29	1.74 to 16.06	.003
	ITT	4	289	241	5.36	1.77 to 16.30	.003
Hypernatremia	ACA	3	164	153	0.73	0.22 to 2.48	.62
	ITT	3	199	192	0.76	0.23 to 2.59	.67
pNa after IV fluid	ACA	6	168	167	−2.09	−2.91 to −1.28	<.0001
	Imputation	11[c]	196	197	−1.54	−2.34 to −0.74	.0002
pNa change	ACA	6	115	107	−3.49	−5.63 to −1.35	.001
	Imputation	11[c]	140	133	−2.24	−3.88 to −0.57	.008

ACA, available case analysis; ITT, intention to treat; WMD, weighted mean difference.

[a] Number of children receiving hypotonic IV solutions.

[b] Number of children receiving isotonic IV solutions.

[c] Imputed missing data were analyzed as separate studies.

imputation 'makes stuff up' in a way that doesn't affect the data but allows other real data from the same pt to be used

pNa changes, and fluid restriction may not satisfy a child's daily requirement. Five of the included studies exclusively enrolled children undergoing surgery,[13,15,16,20] and 1 exclusively enrolled children with illnesses not requiring surgery.[14] Separate analyses showed that hypotonic solutions were associated with increased risk of hyponatremia in each of the populations (data not shown). Four of the included studies enrolled both surgical and nonsurgical patients.[10–12] Yung et al found that surgical patients tended to have a greater fall in pNa than nonsurgical patients (–2.3 mmol/L, 95% CI –4.6 to 0.1, $P = .057$).[10] Three studies also evaluated the influence of mechanical ventilation. They found no difference in pNa and pNa changes after fluid treatment between ventilated and nonventilated patients.[10,12]

DISCUSSION

Our systematic review and meta-analysis of isotonic versus hypotonic maintenance IV fluids in hospitalized children act as an update of previous reviews.[6,22–24] With 10 published RCTs involving 855 subjects, we confirmed the early finding that hypotonic maintenance IV fluid was a risk factor for hospital-acquired hyponatremia for pediatric patients. The review by Choong et al calculated an odds ratio of 17.2 for developing hyponatremia with hypotonic fluids,[6] which was much higher than ours of 3.49 (RR 2.24). Inclusion of retrospective studies and rehydration RCT was likely to contribute to this disparity. Because severe hyponatremia is more strongly associated with symptoms and complications, we also calculated pooled RR of developing severe hyponatremia, whereas previous reviews did not do so because of lack of data at that time.[6] The meta-analysis showed that hypotonic maintenance IV fluids significantly increased the risk of severe hyponatremia in hospitalized children. Such findings raise the possibility that hypotonic maintenance IV fluids could increase hyponatremia-associated death and severe complications such as hyponatremic encephalopathy. Reports of death or neurologic injury as a result of hospital-acquired hyponatremia in children receiving hypotonic IV fluids are also accumulating.[19,31–35] However, in the 855 subjects of the included 10 RCTs, cases developing such severe conditions were too scant to draw a conclusion. One explanation is that such cases are rare and the sample size was not large enough. Another is that participants in the included studies were tested for pNa more frequently than

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those in common practices and therefore were immediately treated before complications occurred.

Hyponatremia occurs due to a deficit in sodium, excessive water intake, or impaired ability to excrete free water.[6,9] The sodium intakes in each group of the included RCTs were well within the daily requirements.[36] In the healthy state, humans can excrete excessive fluid to maintain sodium and water homeostasis. Therefore, the development of hyponatremia was contributed to the impaired ability to excrete free water when hypotonic fluids were administered.

ADH increases the permeability of collecting duct cells in the kidney, leading to retention of free water.[37] Hospitalized children often have ≥1 stimuli (such as postoperative state, blood loss, vomiting, and pain) for excess ADH.[9,38] This is thought to contribute to impaired ability to excrete free water. Thus, hypotonic fluids, with more free water than isotonic fluids, are more likely to cause a positive balance of free water in these pediatric patients. Choong et al observed elevated ADH levels in those developing hospital-acquired hyponatremia regardless of fluid type,[15] suggesting the underlying role of excess ADH in another way. Because of this role, isotonic fluids are not exempt from the risk of developing hyponatremia, although the risk is lower compared with hypotonic fluids.

We are confident in the finding that hypotonic IV fluids were more likely than isotonic IV fluids to cause hyponatremia in hospitalized children. First, the meta-analysis results of hyponatremia, severe hyponatremia, and pNa and pNa changes after fluid therapy are consistent. Second, the results from sensitivity analysis by missing data are similar to those using analysis of available cases. Two studies with special situations also did not affect the results.[13,14] Third, there was no obvious heterogeneity among the included RCTs. The main heterogeneity in the analyses of pNa and pNa changes came from an RCT with a small sample size.[20] Fourth, we adopted a random-effects model in all meta-analyses. This model produces more conserved results than the fixed-effects model.[26,27,39] Many observational studies suggested that isotonic fluids are superior to hypotonic fluids in hospitalized children.[17–19,40–42] These studies were not included in the current meta-analysis because they did not meet the predefined criteria. However, the findings from these studies are consistent with our findings. In addition, 1 RCT with a substantial proportion of patients with preexisting hyponatremia at the baseline showed that isotonic fluids could correct preexisting hyponatremia.[43]

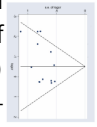
The finding that hypotonic IV fluids were more likely than isotonic IV fluids to develop hyponatremia in hospitalized children may be applicable to a range of settings: restricted fluids or fluids at full rate, medical or surgical patients, and receiving or not receiving mechanical ventilation. Yung et al observed a greater fall of pNa in surgical patients than in medical patients, but their study lacked a description of medical conditions,[10] and hyponatremia is common in patients with infection (especially severe infection) and pulmonary disease (hypoxemic state).[9,44] In surgical patients, it is not uncommon to develop hyponatremia in the postoperative state because of the multiple stimuli for ADH that are present, such as subclinical fluid deficit, pain, nausea, vomiting, and narcotic use.[9] Most participants in this meta-analysis were surgical pediatric patients. Thus, our findings are more applicable to this population.

how many strengths do they cite?

The strength of the review was based on a comprehensive search strategy, explicit criteria for selection of relevant studies, assessment of risk of bias, data analysis strictly following the Cochrane Handbook,[26] and the compliance of the report with the PRISMA guidelines.[25] All included studies were RCTs, making the evidence stronger than previous reviews. However, we note 2 caveats regarding this review. First, only published studies were included. This may introduce a publication bias. Another is the presence of obvious variances among patient characteristics including differing IV fluid types such as 0.45% saline and 0.18% saline, formulas for calculating the rate of IV fluids in different studies, durations of administration, and study quality. Additionally, the sample size was small in most included studies.

how many limitations? (they call them 'caveats')

do you remember what the plot used to detect publication bias is called?



Overall, isotonic fluids are safer than hypotonic fluids in hospitalized children requiring maintenance IV fluid therapy in terms of pNa levels. However, there is no ideal IV fluid for all children in terms of composition of fluid (0.9% saline/Hartmann's, etc) and the rate and duration of administration. pNa needs to be monitored when IV fluids are administered. At present, isotonic fluids may be a better choice than the traditional recommendations.

Dr. Michael Moritz from Childrens Pittsburgh has been like a lone voice in the wilderness for the past 20 years about this topic. He'll tell anyone who will listen that Holliday-Segar should no longer be taught to pediatric housestaff. Maybe that will come true once the Harriet-Lane stops giving the HS-Formula front and center coverage in the Fluids & Electrolytes Section

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oldie but goodie. Free lottery ticket to first person to text me the first names and institution of these 2 authors

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this is from the orginal Holliday-Segar paper from 1957 (ref #1 above). Joel Labow was a teenager reading beat literature back then.

824 HOLLIDAY – WATER IN PARENTERAL FLUID THERAPY

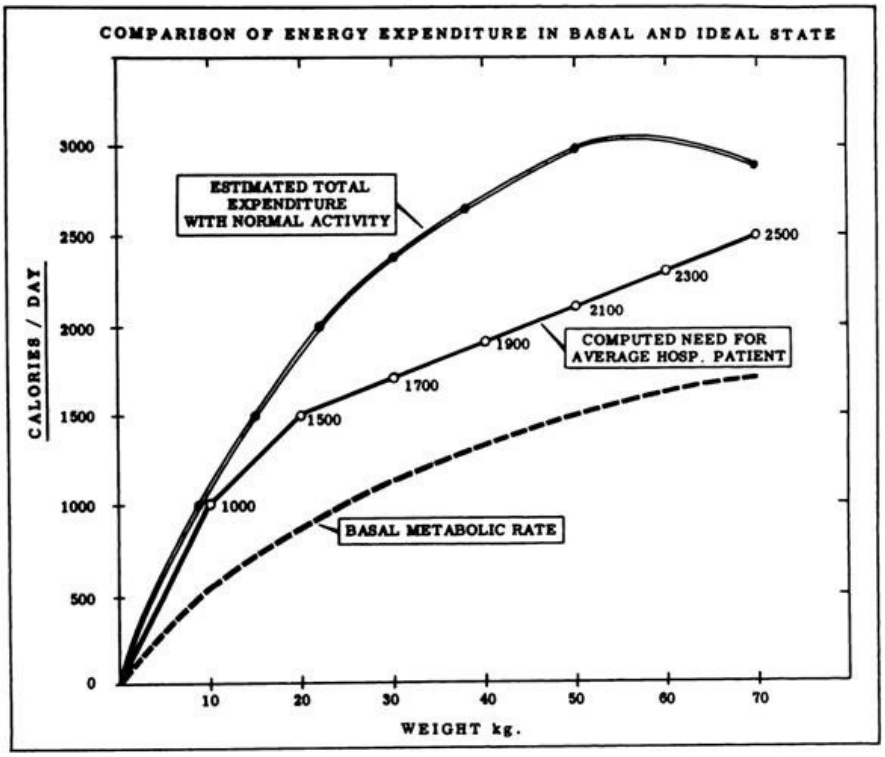

FIG. 1. The upper and lower lines were plotted from data of Talbot.[5] Weights at the 50th percentile level were selected for converting calories at various ages to calories related to weight. The computed line was derived from the following equations:

1. 0-10 kg—100 cal/kg.
2. 10-20 kg—1000 cal + 50 cal/kg for each kg over 10 kg.
3. 20 kg and up—1500 cal + 20 cal/kg for each kg over 20 kg.

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