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Review

Perioperative fluid management in children: an updated review

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Abstract

Background: **Perioperative fluid management in children has been a major topic for debate.**
Objectives: **Our aim is to review the current evidence on perioperative fluid management in children including: type of fluid, administration rates, preoperative fluid intake and monitoring techniques.**
Design: **Narrative review.**
Method: **Following the PRISMA-S guidelines we performed a search (2010-March 2022) in databases Medline (through PubMed) and Cochrane Library. 4297 citations were found and screened by two independent researchers. After screening, 64 articles were withheld for our review.**
Results: **The perioperative administration of isotonic fluids is safer than hypotonic solutions, concerning the development of hyponatremia. A balanced isotonic solution with 1-2,5% glucose should be used as perioperative maintenance IV fluid in children (1 month to 18 years). Colloids can be used in children when inadequate effect in volume correction is achieved with crystalloids. The preferred synthetic colloid for children is a third generation HES in a balanced solution. To date, most clinicians use the "4-2-1 rule" for calculating fluid rate. This may not be the optimal fluid rate, as little research has been done. Preoperative fasting for clear fluids should be limited to 1 hour, children should even be encouraged to drink up until 1 hour before induction. Respiratory variation of aortic blood flow peak velocity (ΔVpeak) with echocardiography is currently the most reliable technique for evaluating fluid responsiveness in children.**

Keywords: **Anesthesia, Perioperative Care, Pediatrics, Isotonic Solutions, Hemodynamic Monitoring.**

Introduction

Fluid administration is a key component in perioperative care. Maintaining the physiological state with normal hydration status for adequate tissue perfusion and normal metabolic function is one of our main goals in perioperative anesthetic care. Perioperative fluid management in children has been a topic for debate in the last three decades.

The fluid requirements in hospitalized children were originally described by Holliday and Segar in 1957[1]. Their formula for an ideal intravenous (IV) maintenance fluid in children was based on the consistency of breast milk and cow's milk, with the required administration rate based on energy expenditure per kilogram of body weight. This has led to the general use of a hypotonic fluid mixture with high glucose content (5%), administered at a rate that is now well known as the "4-2-1 rule".

The tonicity of IV fluids is defined in relation to plasma tonicity. When describing a solution as isotonic or hypotonic, one should consider its in vivo tonicity or osmolality[2]. Often the in vitro tonicity is displayed on product information labels (Table I). Some mixed solutions might have a different tonicity in plasma than their in vitro tonicity. Solutions with high glucose content often have a lower tonicity after infusion, because glucose is rapidly taken into cells for metabolism, inducing more free water content and lower in vivo tonicity. As sodium is the main osmotically active electrolyte in plasma, fluids are considered isotonic when containing a similar concentration of sodium to plasma, while hypotonic fluids contain less sodium. Mcnab et al. considered fluids with a sodium concentration of 125 to 160 mmol/L as isotonic or near isotonic and solutions with a sodium concentration of < 125 mmol/L as hypotonic[3].

Table I. — Composition of commercially available IV fluids in Belgium.

Fluid solutions	Elektrolytes (mmol/L)					Metabolic anions (mmol/L)						Glucose (g/l)	pH	Osmolality (mOsm/kg)
	Na+	K+	Ca++	Mg++	Cl-	Bicarbonate	Lactate	Acetate	Gluconate	Malate	HPO4--			
Plasma	135-145	3,5-5	2,0-2,5	1,0-1,8	98-110	22-29	0,5-1,3						7,36-7,44	303
Unbalanced														
NaCl 0,9%	154				154								±5,5	308
Glucose 5%												50	±4,2	278
Glucose 10%												100	3,5-6,5	555
Glucose 5% + NaCl 0,9%	154				154							50	3,5-6,5	585
Glucose 5% + NaCl 0,45%	77				77							50	3,5-6,5	285
Glucose 5% + NaCl 0,3% + KCl 0,3%	51	40			91							50	±4,5	460
Balanced														
Plasmalyte A	140	5		1,5	98			27	23				±7,4	295
Plasmalyte 148 + glucose 5%	140	5		1,5	98			27	23			50	4,0-6,0	572
Hartmann	131	5	2		111		29						5,0-7,0	278
Hartmann + Glucose 5%	131	5	2		111		29					50	4,0-6,5	555
Sterofundin ISO	145	4	2,5	1	127			24		5			5,1-5,9	309
Sterofundin B	53	24		2,5	50		25				7,3	50	4,0-7,0	444
Hypotonax	25	20		1,5	22		25				3	50	±5,3	372
Isotonax	140	10	2,5	1,5	103		55						±6,3	312
Isotonax-glucose 5%	143	10	2,5	1,5	103		55					50	±5	592
Glucion 5%	54	26		2,6	55		25				6,2	50	4,0-5,2	447
Glucion 10%	54	26		2,6	55		25				6,2	100	4,0-5,2	725
Kidialyte	140	4	1	1	118			30				10	5,3-5,7	351
Colloids														
Voluven 6% (HES 130/0,4; 60 g/L))	154				154								4,0-5,5	308
Venohes (HES 130/0,4, 60 g/L)	154				154								4,0-6,5	309
Gelofusine (GEL 40 g/L)	154				120								±7,4	274
Volulyte 6% (HES 130/0,4; 60 g/L)	137	4		1,5	110			34					5,7-6,5	286
Tetraspan 6% (HES 130/0,4; 60 g/L)	140	4	2,5	1	118			24		5			5,6-6,4	296
Geloplasma (GEL 30 g/L)	150	5		1,5	100		30						5,8-7,0	295

Abbreviations: HES 130/0,4: Hydroxyethyl starches with their respective average molecular weight (130 000 Da) and their degree of molar substitions, GEL: succinylated gelatine.

The use of hypotonic fluids has issued some problems in the past as there were several reports of postoperative hyponatremia with severe neurological morbidity and even death, secondary to hyponatremic cerebral oedema, in the 1990's[4,5]. Luckily these incidents are rare as most healthy children have normal kidney function. The reduced plasma osmolality can thus be compensated by an

increased excretion rate of free water. Critically ill children or children experiencing moderate to high levels of stress with major surgery, have significantly higher antidiuretic hormone (ADH) secretion. As a result, in these cases the administration of hypotonic fluids may lead to a higher risk of hyponatremia[5]. Children are at increased risk of sequelae from hyponatremia, because of their increased brain-to-skull ratio and less cerebrospinal fluid volume[6]. Ten years ago, Najafi et al. published the Belgian

recommendation statement, concerning several aspects of perioperative fluid management in the pediatric population. One of the main points was a switch to using a balanced isotonic fluid with lower glucose content (1 to 2,5%)[7].

Our aim is to review and summarize the current evidence on perioperative fluid management in children (one month to eighteen years) and to look for limitations in the literature as a base for future research. Our focus will not only be on the type of fluid (isotonic vs. hypotonic, glucose content, colloids, etc.), but also fluid administration rate, preoperative oral fluid intake (fasting) and monitoring techniques for fluid requirements. We will specifically include electrical bioimpedance monitoring in our search as this is part of a future research project in our hospital.

Methods

A systematic approach was applied in our literature search for this narrative review to provide ample information, following the "Preferred Reporting Items for Systematic reviews and Meta-analyses Statement" (PRISMA-S) guidelines.

Researching perioperative fluid management in children, we searched for different types of IV fluid (hypotonic, isotonic, glucose-containing solutions and colloids) and infusion rates used in the perioperative setting. Also fluid rate, preoperative fasting for fluids and hemodynamic monitoring techniques (invasive and non-invasive) for guidance of IV fluid management were included in our search. A specific search for bioimpedance monitoring was included as this is the subject of a future study in our center. Pediatric patients aged one month to eighteen years undergoing surgery were included. The following search string was constructed and implemented in the electronic databases Medline (through Pubmed) and Cochrane library: (Pediatric) AND ((perioperative fluid management) OR (IV fluid) OR ((IV fluid) AND perioperative) OR ((IV fluid) AND Anesthesia) OR (fluid resuscitation) OR (fluid rate) OR (fluid respon*) OR (crystalloids) OR (colloids) OR (anesthesia AND (fluid management)) OR (Hemodynamic monitoring) OR (bioimpedance monitoring)).

In our first search the publication date filter was set between January 2010 and January 2021. Later this was updated by rerunning the search until March 2022 in all databases. All types of articles were included. A full text filter and English language filter were used to ensure ample information for every search result. After elimination of duplicates, all citations were manually screened by two authors M.B. and S.S. While screening by title, only the citations that were withheld by both reviewers, were used for further screening. In the next phase, screening by abstract, the articles that were reserved by either of the two independent reviewers, were considered for further evaluation of full text. Any discrepant articles were thoroughly discussed and thereby in- or excluded. Likewise, full text articles were screened, and the quality assessed by both independent reviewers. Exclusion criteria were cardiac surgical patients, patients with acute or chronic kidney disease, metabolic syndromes and sepsis, as these patients have different hemodynamic and fluid physiology requiring specific considerations in fluid management. Another reason for exclusion was articles related to transfusion of blood products, as this was not the scope of our research. Additional articles were included through browsing cited reference lists.

Results

The primary search in Medline (through Pubmed) and Cochrane library, showed a total of 3378 citations. These were checked for duplicates, leaving 3366 citations eligible for screening. An additional 931 articles were added after a search update in March 2022. A total of 4297 articles were then further screened for title and abstract. 4191 articles were excluded, as these articles simply did not answer the clinical question or met any of the exclusion criteria. Consequently, the remaining 106 full texts were evaluated by both reviewers for eligibility, 47 articles were then excluded. After browsing the reference lists, an extra 5 articles were included. Thus, a total of 64 articles were finally included in this study. The full flowchart of the executed data search can be found in Figure 1. In the following a subdivision is made into the categories: fluid composition (isotonic vs. hypotonic solutions, glucose and balanced solutions), colloids, fluid rate, fasting for clear fluids and fluid responsiveness.

1. Fluid composition

Isotonic vs. hypotonic solutions

A European consensus statement by Sümpelman et al. in 2011 stated that a balanced isotonic fluid with less glucose (1-2,5%) should be used

for intraoperative fluid in children instead of the traditionally used hypotonic formula with glucose 5% to reduce the risk of hyponatremia[8]. We found several RCT's confirming this statement[9-11]. Moreover we found two large meta–analyses investigating this.

A Cochrane collaboration research group, led by McNab S. found convincing evidence that when using isotonic solutions there is a lower risk of developing hyponatremia, defined as plasma natrium concentration (pNa) of <135 mmol/L, in comparison with hypotonic solutions. The risk for hyponatremia was halved from 34% for hypotonic solutions to 17% for isotonic solutions (RR 0,48; 95% Confidence Interval (CI) 0,38-0,60)[3]. Mcnab et al. also investigated the risk of developing hypernatremia (pNa >145mmol/L). They found a slightly higher number in the isotonic population compared to the hypotonic population (4% versus 3%, RR 1,24; 95%CI 0,65-2,38, low quality evidence). McNab et al. state that isotonic solutions are protective for hyponatremia in comparison to hypotonic solutions. Tonicity of fluids used should be as close to plasma tonicity as possible[3].

Wang et al. (2014) also conducted a meta-analysis comparing isotonic versus hypotonic fluids in developing hyponatremia[4]. In this systematic review a distinction was made between hyponatremia, defined as pNa <136 mmol/l, and severe hyponatremia, defined as pNa <130 mmol/L. When hypotonic fluids were used, this analysis shows a significant risk for hyponatremia (RR 2,24; 95% CI 1,52-3,31) and an even higher risk for developing severe hyponatremia (RR 5,29; 95% CI 1,74-16,06). No significant difference could be found between the two interventions for the development of hypernatremia (RR 0,73; 95% CI 0,22-2,48).4 Both research groups found a big variety in IV types used for comparison. They state that there is no one ideal IV fluid composition for all patients[3,4].

Lastly, Kim et al. (2020) found a positive effect on postoperative pain with isotonic compared to hypotonic fluids[6]. They investigated the effect of intravenous tonicity on postoperative pain and opioid use in children. They suggest that the higher pain scores and opioid use may also be attributed to hyponatremia causing more discomfort and irritability. Further research is necessary, as this trial had a small number of patients, and no other trials were found on this subject.

Glucose

Glucose is important in the perioperative fluid management in children, as they have less energy reserves compared to adults. Perioperative glucose deficiency may lead to a catabolic state possibly inducing ketoacidosis. Sümpelmann et al. (2011) state that solutions for perioperative maintenance IV fluid should contain 1-2,5% of glucose, reducing the risk of perioperative hypoglycemia and hyperglycemia[8].

Gao et al. (2021) compared the administration of a 1% glucose balanced isotonic solution with lactated Ringer's solution. They found that the lactated Ringer's group had a slight drop in serum glucose in the first hour of surgery compared to the 1% glucose solution. They concluded that the glucose 1% solution could maintain more stable serum glucose levels. In both groups no hyperglycemia or hypoglycemia was observed[12]. In 2010 however, Neville et al. showed, in a prospective RCT, that a glucose 2,5% solution would induce hypoglycemia and/or ketosis in 15% of their population[13].

Sümpelman et al. (2016) state that a glucose 1% solution might be too low in some cases. It is advised that in longer procedures and in children with high risk, i.e. neonates, (ex-)prematures and children with known metabolic diseases, there should be frequent monitoring of plasma glucose and/or ketone bodies. Maintenance fluid glucose content should then be adjusted based on the child's needs[14].

Balanced solutions

Even though it is considered as isotonic, natural saline is often mistakenly called physiological water. It only contains the electrolytes sodium and chloride in a 0,9% concentration. It is not nearly equal to the plasma electrolyte content. Moreover, the high chloride content in natural saline (154 mmol/L) compared to plasma (103 mmol/L) might induce an increase in plasma chloride relative to plasma sodium. This may induce a change in strong ion difference when infused in large volumes, with a subsequent reduction in bicarbonate resulting in a metabolic acidosis. This phenomenon is also known as hyperchloremic acidosis[2,5,7,15].

To prevent hyperchloremic acidosis balanced solutions are used, reducing the chloride content and adding metabolic anions as a buffer. Lactate is added in some solutions. It is metabolized by the liver where an equal amount of bicarbonate is produced. Acetate is metabolized faster and more independent of hepatic function, with lower oxygen consumption. Also, with acetate there is no influence on the diagnostic use of lactate as a marker for low tissue perfusion[2,7,15]. Other metabolic anions as malate and gluconate are also used but were rarely discussed.

There is a vast array of commercially available balanced solutions, each with their own mixture of added electrolytes and metabolic anions (Table I). Other than sodium and chloride, we found

little evidence concerning the addition of other electrolytes. Feld et al. (2018) state that hospitalized children should receive isotonic fluids with appropriate potassium levels, not stating the right amount[16]. Mcnab et al. found that most guidelines recommend that either no potassium or 20 mmol/L should be added[5]. Disma et al. (2014) compared the use of Sterofundin (containing 1 mmol/l of Mg++) versus normal saline (0,9% NaCl) both with 1% glucose added. They found that the serum Mg++ levels were more stable when Sterofundin was used. They found no statistical differences in changes of other electrolytes (calcium 2,5 mmol/L and potassium 4 mmol/L in Sterofundin).17 The addition of calcium may make IV solutions incompatible with citrated blood products and some medications (e.g. ceftriaxone), due to pro-coagulant effects or precipitation respectively[5].

2. Colloids

Colloids are used as volume expanders when inadequate effect in volume correction is achieved with crystalloids. Colloids can be divided into the human derived natural protein albumin and synthetic colloids: Hydroxyethyl starches, gelatins and dextrans. Human albumin (HA) is often considered as the gold standard for colloid therapy. Its use has been reduced since some studies have shown no benefit in effectiveness for volume expansion compared to other colloids. Its increased cost, lesser availability, and fear for transmission of viruses have also contributed to this diminishing use[18,19]. Synthetic colloids are suggested to be more cost-effective than human albumin. There is however some controversy around their use, as they have shown significant adverse reactions in adult populations (e.g. allergy, renal dysfunction, coagulopathy)[14]. Because of their higher incidence of anaphylactoid reactions and other adverse reactions, dextrans have been restrained from use in several countries. Gelatins, derived from bovine collagen, have lower molecular weights and therefore lower oncotic effects. They have shown a safer profile concerning coagulopathy and kidney function. Their incidence of anaphylactic reactions (0,05-0,1%), however, is still higher than other available colloids. Fewer studies have been done with the use of gelatins in children. Thus, their use in children is less frequent than hydroxyethyl starches (HES). Most recent studies concerning colloids in children include the use of third generation low molecular weight HES (130 000 Da). These preparations with lower molecular weight and lower molar substitutions have shown a safer profile than their predecessors in adults[19].

A study from Sümpelmann et al. (2010) showed that HES in a balanced solution are preferred over HES in natural saline, avoiding acid-base and electrolyte disturbances.20 No negative effect of HES (130/0,4) on kidney function was found[21].

Thy et al. (2018) rendered a meta-analysis, researching the overall safety of using 6% low molecular weight HES (130/0,4) in children. There was no significant modification in the amount of administered perioperative fluids, urine output or blood loss and no significant renal toxicity when HES was used. However, they state that included studies were of low quality and their meta-analysis lacks statistical power[22].

Schick et al. (2021), compared the use of HES (130/0,4) and HA in neurosurgery with major blood loss[23]. They found that the HA infusion volumes were substantially greater, and a more positive fluid balance was seen post-surgery in the HA group. This was partly attributed to the fact that HES administration is limited by a maximum dosage, unlike HA. The HA group showed more coagulopathy (decreased fibrinogen, increased aPTT and a higher blood loss during surgery), which could not be found in the HES group. There were no differences in urinary output and kidney function between the two groups. The HA group however showed a shorter ventilation time and length of hospital stay. The study is too weak, however, to show significant evidence in the safe use of colloids[23].

Sümpelmann et al. indicate that the preferred synthetic colloid for children is a third generation HES with a molecular weight of 130 000 Da. It should be administered in boluses of 5-10 mL/kg if clinically needed and a moderate total dose of 10-20mL/kg should be aimed for, never trespassing the max. dose of 30ml/kg[2,14,19].

3. Fluid rate

The "4-2-1 rule" (Table II) was derived from an oral fluid intake of healthy children. Hospitalized children have a higher ADH excretion and thus fluid retention. Therefore, the required fluid rate could be less. McNab states that in most cases where children are not dehydrated, a fluid rate of ½ to ⅔ of the traditionally calculated fluid rate could be enough[5].

Neville et al. (2010) compared two fluid regimens (full or half maintenance rate) and found that children receiving 50% of the standard maintenance rate, following the "4-2-1 rule", were more likely to be dehydrated[13].

Sümpelmann et al. however found, in 2 separate observational studies (2010 and 2011), that a perioperative maintenance rate of 10 ml/kg/h resulted in stable hemodynamic conditions[24,25]. The two studies were performed with a balanced isotonic solution with 1% glucose. This higher fluid rate than

Table II. — Calculation for maintenance fluid rate based on the traditional "4-2-1 rule".

Body weight	Fluid maintenance	
	Daily fluid requirement	Hourly fluid requirement
< 10 kg	100 mL/kg/d	4 mL/kg/h
10-20 kg	1000 mL + 50 mL/kg/d for every kg more than 10 kg	40 mL + 2 mL/kg/h for each kg more than 10 kg
> 20 kg	1500 mL + 20 mL/kg/d for each kg more than 20 kg	60 mL + 1 mL/kg/h for each kg more than 20 kg

the "4-2-1 rule" is suggested to be due to correction for fasting-related fluid deficits. With shortening fasting times this might be debatable.

In two later publications Sümpelmann et al. propose the use of "the rule of 10s" with a background maintenance rate of 10mL/kg/h and additional 10-20mL/kg boluses to compensate for pre-existing fluid deficit or ongoing fluid losses. A maximum of 3 boluses can be administered to avoid interstitial fluid overload, using a balanced isotonic electrolyte solution. An overview of Sümpelmann's fluid therapy proposition is added as Table III.[2,14]

A RCT by Mandee et al. (2014) compared two fluid regimens in major abdominal surgery[26]. A 'fluid restrictive' group using the "4-2-1 rule" with additional boluses based on hemodynamic needs was compared to a 'liberal fluid regimen' using the "4-2-1 rule" with correction for preoperative fluid deficit, an addition of 5mL/kg/h for interstitial space loss and additional boluses. The restrictive group needed more supplemental boluses, concluding that restrictive fluid regimens may not be suitable for the pediatric population[26].

Najafi et al. (2012) proposes to augment the standard maintenance rate with 1 to 15 mL/kg/h, depending on the surgical procedure, to account for fluid loss to the interstitial space, surgical and insensible losses[7].

4. Fasting for clear fluids

Convincing evidence was found for a revised preoperative fasting protocol. Fawcett et al. (2019) and Thomas et al. (2018) both state that the time limit for intake of clear fluids should be reduced to 1 hour (Table IV)[27,28]. The time limit for solid foods however remains unchanged.

Current fasting rules in most hospitals implement a 6-hours limit for solid food and formula milk, 4 hours for breast milk and 2 hours for clear fluids. This is however based on evidence dating back from before 2012. A theoretical 2-hour limit for fluids often leads to an actual fasting time of 6-15 hours.28-31 This can result in a preoperative catabolic state, hypotension after induction and a higher incidence of postoperative nausea and vomiting. Diminishing the fasting time for clear fluids results in less irritability, fear and discomfort during induction and any metabolic effects are minimized[27].

In their updated guidelines (2022), the European Society of Anaesthesiology and Intensive Care (ESAIC) recommend a 1-hour time limit. As for breast milk and formula milk in infants, they recommend a 3- and 4-hour time limit respectively (table 4)[27]. The European Society of Pediatric Anesthetists (ESPA) even advised to encourage clear fluid intake up until 1 hour before scheduled general anesthesia, administering 3mL/kg of clear fluids on admission. These ought to be non-thickened and non-carbonated, e.g. water or diluted apple juice[28]. More strict measures should be taken in case of known preoperative states like diabetic gastroparesis, some gastro-intestinal conditions, severe cerebral palsy, renal failure and certain surgical contraindications[28].

Table III. — Perioperative fluid management with the "rule of 10s" adapted after Sümpelmann et al.[8]

	Solution for infusion	Rate/Repeated bolus
Maintenance rate	Balanced isotonic electrolyte solution with 1-2% glucose	10 mL/kg/h
Fluid bolus	Balanced isotonic electrolyte solution	x 10 - 20 mL/kg
Volume bolus	Albumin, gelatin, HES	x 5 - 10 mL/kg
Transfusion	RBC, FFP, PT	x 10 mL/kg
RBC: red blood cells, FFP: fresh frozen plasma, PT: platelets.		

Table IV. — Updated preoperative fasting rules for elective anesthesia in children based on the new ESAIC guidelines by Frykholm et al.[36]

Age (y)	Solid food	Formula milk	Breast milk	Clear fluids
0-18	6h	4h	3h	1h
Recommended as clear fluids: water, diluted apple juice, sports drinks without fizz				

Postoperative fasting times for clear fluids may also be limited to a minimum. Chauvin et al. (2017) found that early postoperative fluid intake led to less opioid use and less postoperative nausea and vomiting. An early liberal postoperative fluid intake was also advised in the new ESAIC guidelines. There is, however, limited research on this matter[32,33].

5. Fluid responsiveness

It is suggested by some authors that an individualized goal-directed therapy regarding fluid rate could be beneficial in children, but reliable hemodynamic monitoring techniques are still lacking in pediatric anesthesia. Many monitoring techniques used in adults have limited value in children[18,34].

For minor procedures with a normal preoperative hydration status, standard monitoring techniques (pulse oximetry, capnography, non-invasive blood pressure, ECG, etc.) will be sufficient. When in doubt, a capillary or venous blood gas analysis (base-excess, lactate, glucose) can provide added information. In more extensive surgery, placement of arterial or central venous lines is often used for beat-by-beat pressure monitoring and serial blood gas analysis. Pulmonary artery catheters and transpulmonary thermodilution are used on rare occasions[14].

Static variables like heart rate, central venous pressure, pulmonary artery occlusion pressure, etc. are based on a single observation in time. They have no ability to predict fluid responsiveness[35]. The use of dynamic parameters generated from arterial pressure waveforms, like systolic pressure variation (SPV), pulse pressure variation (PPV) and stroke volume variation (SVV), are based on respiratory variability in cardiac preload and therefore cardiac output. They have been established in guiding fluid responsiveness in adults. In children however, none have shown reliability in predicting fluid responsiveness because of higher chest/lung and vascular compliance, lower cardiac compliance and cardiac output in children[35-37]. Pulse contour analysis monitors, like PiCCO™ (Pulsion), Vygon™ (Vytech), and Flotrac™ (Edwards Lifesciences), are derived from the arterial pressure waveform and face similar limitations, showing conflicting results in the pediatric population[36].

As the plethysmographic waveform is derived from changes in vessel volume instead of pressure, the above-mentioned limiting factors could be less influencing. Dynamic parameters derived from plethysmography, like pulse oximeter plethysmograph amplitude variation (ΔPOP) and plethysmography variability index (PVI), show similar effectiveness in predicting fluid responsiveness in adults[38]. A meta-analysis by Desgranges et al. (2016) showed that PVI could be a reliable parameter in predicting fluid responsiveness in children. Given the low number of studies included, with small populations, no definitive conclusions can be made[39]. A later study (2021) by the same authors could not confirm the effectiveness of PVI[40]. The reliability of plethysmography derived parameters can be influenced by sampling site, peripheral perfusion, microcirculation, the use of vasopressors and contact pressure of the probe[36].

Respiratory variation of aortic blood flow peak velocity (ΔVpeak) measured by pulsed wave doppler with transthoracic or transesophageal echocardiography is believed to be the most consistent predictor of fluid responsiveness in mechanically ventilated children[36,36]. A meta-analysis by Desgranges et al. (2016) showed a sensitivity of 92% (95% CI 84,1-96,7), a specificity of 85,5% (95% CI 75,6-92,5) and a diagnostic odds ratio of 50,44 (95% CI 17,70-143,74) for ΔVpeak to predict fluid responsiveness. Flow measurements by ΔVpeak are not affected by arterial compliance or changes in peripheral perfusion. The technique requires a skilled echocardiographer, which may limit its use in everyday practice. There is a great variation in cutoff values of ΔVpeak to discriminate between fluid responders and nonresponders (ranging from 7 to 20%)[41].

ΔVpeak can also be measured via the suprasternal notch view, which has more practicality during surgery compared to the apical 5-chamber view[41,42]. Other variants of this technique have been deduced. Transfontanelle measurement of respiratory variation of carotid artery blood flow peak velocity (ΔVpeak_CA) has been shown useful in several cardiac surgery setups[36,43].

A noninvasive continuous-wave Doppler monitor (USCOM; USCOM Ltd.) was derived from the suprasternal ΔVpeak technique. Stroke volume variation (SVV) measured with USCOM, shows promising ability to predict fluid responsiveness, with a relative ease of use[44]. An older study, however, has shown less reliable values when compared to pulmonary artery catheter cardiac output values[45].

Respiratory variations in inferior vena cava diameter (ΔIVC) is another validated technique for assessing fluid responsiveness in adults. A recent meta-analysis by Orso et al. (2017) however showed that ΔIVC is not a reliable method for predicting fluid responsiveness in children[46].

Continuous blood flow velocity measurement in the descending aorta with an esophageal Doppler system (CardioQ™; Deltex Medical) showed promising results in a study by Weber et al[47]. They found a cutoff value of > 135,5 cm/s to be indicative

to terminate further fluid challenges. Target values may be different in various age groups. The few other studies that were performed could not show similar results[48,49].

Lastly, several noninvasive cardiac output monitors have been produced based on thoracic electrical bioimpedance also known as electrical cardiometry (NICOM™, Cheetah Medical Inc.; Physioflow™, NeuMedDx; ICON™, Osypka Medical Inc.; Aesculon™, Osypka Medical Inc.). Relative phase shifts of either constant or oscillating electrical currents are analyzed when traversing the thorax. Variations in thoracic resistance are then registered due to changes in blood velocity throughout the cardiac cycle[50]. Studies have shown promising results, with good reliability of these monitors in estimating CO and SVV[51-53]. However, most pediatric study populations are small and there is a great variety in validation techniques leading to heterogeneity in results. Their clinical use in the operation room may be limited by interference from monopolar (not with bipolar) electrocauterization and changes in intrathoracic impedance in certain clinical settings (e.g. interstitial edema, open thorax surgery, etc.)[52,53].

Discussion

The evidence is very clear that isotonic solutions are safer than the traditional hypotonic solutions concerning the development of hyponatremia. A balanced isotonic solution with 1-2,5% glucose is recommended as perioperative maintenance IV fluid in children (1 month to 18 years). Its in vivo osmolality should mimic the plasma osmolality as closely as possible. However, a commercially available product with this required content was not yet readily available, forcing anesthesiologists to compose their own mixture with risk of complications[2,7,14]. As of recently, this balanced isotonic fluid with less glucose is commercially available (Table I). Since a commercial product has become available, this should become standard practice in perioperative care for children. However, there is still more research needed in determining the optimal electrolyte composition of such solutions. Careful considerations should be made in the choice of product for different clinical conditions, as the varying combinations of electrolytes, glucose and metabolic anions may have an influence on solution tonicity and/or various metabolic conditions. Regular blood analysis may be necessary in prolonged administration of IV fluids.

Colloids can be used in children when inadequate effect in volume correction is achieved with crystalloids. The preferred synthetic colloid for children is a third generation HES in a balanced solution. However, as there is still ongoing debate about their safety in adult and pediatric populations, care should be taken in the use of colloids in children. More high-quality RCTs should be conducted to further explore their safety in children. We should note that studies concerning colloids often were performed in cardiac surgery settings, which was one of our exclusion criteria for this review. Nevertheless, studies so far often have included small numbers of patients, which leads to lack of statistical evidence.

To date, most clinicians still use the traditional "4-2-1 rule" for calculating fluid rate in maintenance infusion for children. This may not be the optimal fluid rate, as little research has been done in comparing different fluid regimens. This is one of the major interests for future research in perioperative fluid management in children.

There is convincing evidence that preoperative fasting for clear fluids should be limited to 1 hour. Children should even be encouraged to drink small amounts of clear fluids up until 1 hour before induction. The risk for aspiration has been proven to be low in several studies. The "APRICOT" study by Habre et al. shows an allround incidence of 9,3/10.000 (=0,093%) perioperative aspirations, including urgent settings and non-fasted patients[54]. Frykholm et al. (2018) reports an allround incidence of 3/10.000 perioperative aspirations[55]. Beck et al. showed similar results[56]. These low numbers can be attributed to quick gastric emptying of clear fluids, especially in children. Several MRI and ultrasound studies have shown gastric emptying in less than 1 hour after intake of clear fluids (up to 7 mL/kg)[56-58]. Furthermore the consequences of perioperative aspiration of clear fluids are often not deleterious. Rarely there is a need for more than prolonged monitoring or antibiotic therapy[27,32,54]. Thus the new ESAIC on preoperative fasting should be implemented in daily practice (Table IV)[32].

When considering hemodynamic monitoring for fluid management, respiratory variation of aortic blood flow peak velocity (ΔVpeak) with echocardiography is currently the most reliable technique for evaluating fluid responsiveness in children. The optimal cutoff value to determine fluid responsiveness should be further investigated. There are some other promising techniques such as plethysmography variability index, blood flow velocity measurement in the descending aorta with an esophageal doppler and non-invasive cardiac output monitors based on changes in thoracic electrical bioimpedance. Their accuracy should however be further investigated in large patient populations compared with transthoracic echocardiography. It

is advised to use Δvpeak as a standard reference in future studies to compare reliability of other monitoring techniques. The development and testing of hemodynamic monitoring systems for guiding fluid management is of great importance for further research in other fields of fluid therapy in children (e.g. optimization of fluid rate).

A possible weakness of this study is the publication bias, as only published studies were included. Also, by excluding studies concerning cardiac surgery, several useful publications about fluid types and monitoring techniques may not have been considered for this review.

Conclusion

A balanced isotonic solution with 1-2,5% glucose should be used as perioperative maintenance IV fluid in children (1 month to 18 years). Colloids can be used in children when inadequate effect in volume correction is achieved with crystalloids. The preferred synthetic colloid for children is a third generation HES in a balanced solution. To date, most clinicians use the "4-2-1 rule" for calculating fluid rate. This may not be the optimal fluid rate. More research is necessary. Preoperative fasting for clear fluids should be limited to 1 hour, children should even be encouraged to drink up until 1 hour before induction. Respiratory variation of aortic blood flow peak velocity (ΔVpeak) with echocardiography is currently the most reliable technique for evaluating fluid responsiveness in children but is limited in practical use. Other techniques are promising but require further investigation and validation in the pediatric population.

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