Perioperative fluid management in children: can we sum it all up now?

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Purpose of review
The composition and type of intravenous fluids during paediatric anaesthesia have been subjects of debates for decades. Errors in perioperative fluid management in children may lead to serious complications and a negative outcome. Therefore, in this review, historical and recent developments and recommendations for perioperative fluid management in children are presented, based on physiology and focused on safety and efficacy.

Recent findings
Optimized fasting times and liberal clear fluid intake until 1 h improve patient comfort and metabolic and haemodynamic condition after induction of anaesthesia. Physiologically composed balanced isotonic electrolyte solutions are safer than hypotonic electrolyte solutions or saline 0.9% to protect young children against the risks of hyponatraemia and hyperchloraemic acidosis. For intraoperative maintenance infusion, addition of 1–2% glucose is sufficient to avoid hypoglycaemia, lipolysis or hyperglycaemia. Modified fluid gelatine or hydroxyethyl starch in balanced electrolyte solution can safely be used to quickly normalize blood volume in case of perioperative circulatory instability and blood loss.

Summary
Physiologically composed balanced isotonic electrolyte solutions are beneficial for maintaining homeostasis, shifting the status more towards the normal range in patients with preexisting imbalances and have a wide margin of safety in case of accidental hyperinfusion.

Keywords
fluid management, paediatric anaesthesia, physiology, safety

INTRODUCTION

The objective of perioperative fluid management is to maintain or re-establish the normal physiological state in children (normal extracellular fluid volume, normal blood volume, normal tissue perfusion, normal metabolic function, normal electrolyte and acid–base status) [1▪▪]. Traditionally, a maintenance or background infusion is used to meet the normal fluid and glucose requirements over the course of the perioperative fasting time, during which the children are not allowed to drink, supplemented as needed by fluid replacement to maintain the normal extracellular fluid volume and volume replacement to quickly normalize blood volume, for example, in case of circulatory instability and blood loss. The composition (hypotonic or isotonic) and the type (crystalloid or colloid) of intravenous fluids in paediatric anaesthesia have been subjects of debates for decades. Therefore, in this review, historical and recent developments and recommendations for perioperative fluid management in children are presented, based on physiology and focused on safety and efficacy.

CONCEPT OF HOMEOSTASIS

In the early 19th century, the French physiologist Claude Bernard (1813–1878) established the use of scientific methods in medicine, originated the term internal environment ('milieu intérieur') and stated that a free and independent existence of an organism was possible only because of the stability of the

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KEY POINTS

- Optimized preoperative and postoperative fasting times are important to avoid patient discomfort, iatrogenic dehydration and catabolic state.
- Balanced isotonic electrolyte solutions are recommended for fluid replacement in all age groups to avoid both hyponatraemia and hyperchloraemic acidosis.
- For intraoperative maintenance infusion, addition of 1–2% glucose is recommended to avoid hypoglycaemia, lipolysis or hyperglycaemia.
- Modified fluid gelatine or hydroxyethyl starch in balanced electrolyte solution can safely be used to quickly normalize blood volume in case of perioperative circulatory instability and blood loss.

'milieu intérieur'. Later on, this concept was expanded by the American physiologist Walter Cannon (1871–1945), who coined the term 'homeostasis' as a system of active and passive mechanisms to maintain a steady state within an organism, and another American physiologist, Arthur Guyton (1919–2003), included this in a major textbook of physiology as a control system that tends to minimize disturbances to the internal environment [2]. As a consequence, the paediatric anaesthetist should understand the underlying physiological and biochemical systems and favour techniques, drugs and fluids which are appropriate to maintain or re-establish the patient's homeostasis perioperatively. Of importance, this strategy was also included in the present European SAFETOTS initiative, which is a multimodal approach to improve the safety in paediatric anaesthesia suggesting a 10-N paediatric anaesthesia quality checklist for a better maintenance of the perioperative homeostasis of children [3▪].

HISTORICAL DEVELOPMENT OF ELECTROLYTE SOLUTIONS FOR PERIOPERATIVE FLUID REPLACEMENT

The intravenous infusion of saline solution was first reported in 1831 by the British physician Thomas Latta in patients dehydrated by cholera. In 1882, the British clinician and physiologist Sydney Ringer added potassium and calcium to a saline solution to sustain the contractility of isolated frog hearts. In 1883, the Dutch biochemist Hartog Hamburger performed experiments with red blood cells in varying concentrations of salt and showed that saline 0.9% was isotonic with human blood. In 1932, the American paediatrician Alexis Hartmann modified Ringer's solution by adding the stable metabolizable anion lactate (=Ringer's lactate) as a precursor of the unstable bicarbonate to combat metabolic acidosis in children with diarrhoea [4]. In 1923, the American physiologist Gamble and paediatrician Darrow described the electrolyte and acid–base composition of extracellular fluid by 'Gamblegrams' and initiated intravenous fluid therapy as an effective treatment for diarrhoeal dehydration [5]. In recent decades, several manufacturers have introduced balanced isotonic electrolyte solutions mimicking the composition of extracellular fluid more closely, containing acetate as bicarbonate precursor. Table 1 shows the composition of saline 0.9%, Ringer's, Hartmann's (=Ringer's lactate) and a balanced isotonic electrolyte solution in chronological order describing the stepwise approximation towards the composition of plasma and extracellular fluid.

HISTORICAL DEVELOPMENT OF ELECTROLYTE SOLUTIONS FOR INTRAOPERATIVE MAINTENANCE INFUSION

In 1957, the American paediatricians Holliday and Segar first provided calculations for 'the maintenance need for water in parenteral fluid therapy' and derived the 4-2-1 rule from the caloric expenditure of children: 4 ml/kg/h for the first 10 kg of weight, 2 ml/kg/h for the next 10 kg, and 1 ml/kg/h for each kilogram thereafter [6]. They then analyzed the composition of human and cow's milk to calculate the maintenance needs for electrolytes, and in the following years this led to the common practice of using hypotonic electrolyte solutions with glucose 5% for maintenance infusion in children [7]. In the 1990s, this practice was questioned because of reports about postoperative hyponatraemic encephalopathy as a consequence of infusion of hypotonic electrolyte solutions and stress-induced elevated antidiuretic hormone (ADH) levels leading to cerebral oedema and respiratory insufficiency [8▪▪,9▪]. In addition, other authors found that the intraoperative use of electrolyte solutions with glucose 5% was associated with hyperglycaemia, whereas the use of lower glucose concentrations of 1–2% was sufficient to maintain plasma glucose concentrations within the physiological range and to prevent a compensatory increase in lipid mobilization [10]. As a consequence, several working groups recommended the use of isotonic electrolyte solutions with lower glucose concentrations of 1–2% for intraoperative maintenance infusion as a pragmatic approach to prevent any hyponatraemia, hypoglycaemia, lipolysis and hyperglycaemia (e.g. [11,12]). Unfortunately, at that time, there was no European marketing authorization for such a solution, and therefore, a consensus statement on the composition of an appropriate intraoperative solution for infusion in

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Table 1. Osmotically active components of plasma and various electrolyte solutions for fluid replacement in children

	Unit	Plasma	NaCl[a]	Ringer	RL[b]	BS[c]
Cations						
Na^+	mmol/l	142	154	147	130	145
K^+		4.5	–	4	5	4
Ca^{2+}		2.5	–	2.3	1	2.5
Mg^{2+}		1.25	–	–	1	1
Anions						
Cl^-	mmol/l	103	154	156	112	127
HCO_3^-		24	–	–	–	–
Acetate		–	–	–	–	24
Lactate		1.5	–	–	27	–
Malate		–	–	–	–	5
Theoretical osmolarity[d]	mOsmol/l	291[e]	308	309	276	309
In-vivo osmolality[f]	mOsmol/kg H_2O	288	286	287	256	287
Potential base excess	mmol/l	0	−24	−24	+3	+10

[a]Saline 0.9%.
[b]Ringer's lactate.
[c]Balanced isotonic electrolyte solution.
[d]Σ(cations + anions).
[e]Including glucose, urea and organic acids.
[f]Osmolarity × osmotic coefficient 0.926/water content 0.997.

children was published, recommending an osmolality close to the physiologic range in children to avoid hyponatraemia, an addition of 1–2% instead of 5% glucose to avoid hypoglycaemia, lipolysis or hyperglycaemia and metabolic anions (e.g. acetate, lactate or malate) as bicarbonate precursors to prevent hyperchloraemic acidosis [13▪]. In the meantime, a European marketing authorization for a balanced isotonic electrolyte solution with glucose 1% was granted, and Table 2 shows the composition of several hypotonic

Table 2. Osmotically active components of plasma and various electrolyte solutions for intraoperative maintenance infusion in children

	Unit	Plasma	HEG-5[a]	Polyionique B66	RL-G1[b]	BS- G1[c]
Cations						
Na^+	mmol/l	142	70	120	130	140
K^+		4.5	2	4.2	5	4
Ca^{2+}		2.5	1.25	2.8	1	2
Mg^{2+}		1.25	0.5	–	1	2
Anions						
Cl^-	mmol/l	103	65.5	108.3	112	118
HCO_3^-		24	–	–	–	–
Acetate		–	–	–	–	30
Lactate		1.5	–	20.7	27	–
Malate		–	10	–	–	–
Glucose	mmol/l	2.78–5	277.5	50.5	55.5	55.5
Theoretical osmolarity[d]	mOsmol/l	291[e]	151	258	276	296
In-vivo osmolality[f]	mOsmol/kg H_2O	288	140	240	256	275
Potential base excess	mmol/l	0	−4	−3.3	+3	+6

[a]Hypotonic electrolyte solution with glucose 5%.
[b]Ringer's lactate with glucose 1%.
[c]Balanced electrolyte solution with glucose 1%.
[d]Σ (cations+anions) without glucose.
[e]Including glucose, urea and organic acids.
[f]Osmolarity × osmotic coefficient 0.926 /water content 0.997.

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and isotonic electrolyte solutions with different glucose concentrations in chronological order describing a stepwise approximation towards the composition of plasma and extracellular fluid. The theoretical in-vitro osmolarity (mOsmol/l) of all presented solutions is hypertonic because of the glucose content. After infusion, the glucose rapidly enters the cells to be metabolized, and the risk of hyponatraemia and hyponatraemic encephalopathy increases when the remaining in-vivo osmolality without glucose is low (mOsmol/kg H_2O; Table 2). As a consequence, the Pharmacovigilance Risk Assessment Committee (PRAC) recommended to include special warnings and precautions for use in the Summaries of Product Characteristics for glucose-containing electrolyte solutions (https://www.ema.europa.eu/documents/prac-recommendation/prac-recommendations-signals-adopted-3-6-july-2017-prac-meeting_en.pdf, accessed 30 November 2018).

HISTORICAL DEVELOPMENT OF COLLOIDS FOR PERIOPERATIVE VOLUME REPLACEMENT

The perioperative use of colloids has been the subject of debates for decades. Traditionally, natural colloids (e.g. albumin) were used most often in paediatric anaesthesia, but in the 1990s, albumin was gradually replaced by gelatine (GEL) or hydroxyethyl starch (HES) because of lower costs and easier storage [14–16]. In the following years, the use of third generation HES (molecular weight 130 000 Da) gained popularity [17], but recently several randomized clinical studies showed that renal failure occurred more frequently in adult intensive-care patients with sepsis after HES infusion (e.g. [18]). Interestingly, in paediatric animal studies, renal function was normal after both moderate (20 ml/kg) and high doses (50 ml/kg) of GEL and HES [19,20]. Haemostasis was comparable with a control group after moderate doses (10–20 ml/kg), but significantly impaired after high doses (40 ml/kg) of GEL and HES [21]. In clinical studies, HES 130 was well tolerated and effective in children with normal renal function undergoing major paediatric [22] and paediatric cardiac surgery [23], and a recent meta-analysis found no impairment of renal function, blood loss and transfusion volume in children with perioperative HES infusion [24▪]. Nevertheless, in 2018, the European Medicines Agency considered removing HES-containing solutions from the market, and HES is now contraindicated in critically ill patients with sepsis or burns. The manufacturers decreased the maximum daily dose from 50 to 30 ml/kg. In adults, the incidence of anaphylactoid reactions is higher with GEL as compared with HES [25]. In children, the incidence is possibly lower, but no safety studies with GEL in children are currently available. GEL and HES were initially dissolved in saline 0.9%, but presently both are also available in a balanced isotonic electrolyte solution (Table 3) to avoid iatrogenic acid–base and electrolyte alterations [26▪].

Table 3. Osmotically active components of plasma and gelatine and hydroxyethyl starch in saline or balanced isotonic electrolyte solution for volume replacement in children

			GEL[a]		HES[b]	
Solution	**Unit**	**Plasma**	**Saline**	**Balanced**	**Saline**	**Balanced**
Cations						
Na^+	mmol/l	142	154	151	154	140
K^+		4.5	–	4	–	4
Ca^{2+}		2.5	–	1	–	2.5
Mg^{2+}		1.25	–	1	–	1
Anions						
Cl^-	mmol/l	103	120	103	154	118
HCO_3^-		24	–	–	–	–
Acetate		–	–	24	–	24
Lactate		1.5	–	–	–	–
Malate		–	–	–	–	5
Theoretical osmolarity[c]	mOsmol/l	291[d]	274	284	308	304
In-vivo osmolality[e]	mOsmol/kg H_2O	288	254	264	286	282
Potential base excess	mmol/l	0	−24	0	−24	+10

[a]Gelatine.
[b]Hydroxyethyl starch.
[c]Σ (cations + anions).
[d]Including glucose, urea and organic acids.
[e]Osmolarity × osmotic coefficient 0.926/water content 0.997.

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PHYSIOLOGICAL ASPECTS

From a clinical point of view, the internal environment is represented by plasma and extracellular fluid (ECF). Small children have a larger extracellular fluid volume than adults (e.g. premature infants 60%, neonates 40%, infants 30%, adults 20% of body weight) [27], but the composition of plasma and ECF is similar across all age groups. Therefore, the same solutions for infusion as for adults can be used for perioperative fluid replacement in children. The osmotic activity of an electrolyte solution is described in terms of its osmolality (mOsmol/kg H_2O) or osmolarity (mOsmol/l). By pure chance, the actual osmolality of plasma (288 mOsmol/kg H_2O) is practically identical to the theoretical osmolarity (291 mOsmol/l) calculated from its analytical composition [28▪], and this value (288 mOsmol/kg H_2O) should be used as a reference point for an isotonic or iso-osmolal electrolyte solution [29]. Saline 0.9% has a theoretical osmolarity of 308 mOsmol/l (=154 mmol/l Na^+ + 154 mmol/l Cl^-) or an actual (real) osmolality of 286 mOsmol/kg H_2O (=theoretical osmolarity 308 mOsmol/l × osmotic coefficient 0.926/water content 0.997). The difference can be explained by the fact that a part of the electrolytes infused are not osmotically effective because of absorption on proteins and cell membranes [28▪]. As compared with plasma and ECF, conventional Ringer's lactate (=Hartmann's) solution is somewhat hypotonic (276 instead of 308 mOsmol/l or 256 instead of 288 mOsmol/kg H_2O), while saline 0.9% or Ringer's solution contain too much chloride (154 instead of 95–106 mmol/l, Table 1). Therefore, infusion of large volumes may reduce the osmolality or result in hyperchloraemic acidosis. The potential base excess (BE_{pot}) of an electrolyte solution indicates the amount of HCO_3^- that can potentially be released in the body after metabolization of the anions infused (e.g. acetate, lactate, malate). A solution with BE_{pot} less than 0 mmol/l has an acidotic effect and a solution with BE_{pot} greater than 0 mmol/l an alkalotic effect, whereas one with $BE_{pot} = 0$ mmol/l has no effect on the patient's acid–base balance [28▪]. As compared with lactate, metabolization of acetate is significantly faster, more independent of hepatic function, with a lower increase in oxygen consumption and no interference with the diagnostic use of lactate as a marker of low tissue perfusion [28▪]. In case of preexisting imbalances, balanced isotonic electrolyte solutions shift the status more towards the normal range. These properties are favourable to maintain the homeostasis perioperatively and provide additional safety in case of accidental hyperinfusion [30▪]. Acetate-containing balanced isotonic electrolyte solutions are also compatible with most anaesthetic drugs except phenytoin and diazepam [31].

PREOPERATIVE FASTING

Clinical studies have shown that excessive fasting is not uncommon in children presenting for surgery (e.g. [32]). Prolonged preoperative fasting times were associated with ketoacidosis [33], and optimized preoperative fasting times decreased the ketone body concentration and the incidence of hypotension (mean arterial blood pressure <40 mmHg) after induction of anaesthesia in children younger than 3 years of age [34▪]. Shortened fasting times for clear fluids until the children are called to the operating suite improved the perioperative experience for parents and children without increasing the incidence of pulmonary aspiration [35▪▪], and 1 h of clear fluid fasting did not alter gastric pH or residual volume as compared with 2 h of fasting [36]. As a consequence, the Association of Paediatric Anaesthetists of Great Britain and Ireland, the European Society for Paediatric Anaesthesiology, and *L'Association Des Anesthésistes-Réanimateurs Pédiatriques d'Expression Française* endorsed a consensus statement that advocates reducing the fasting time for clear fluids from 2 to 1 h [37▪]. In the guidelines for perioperative fluid therapy in children by the Association of the Scientific Medical Societies in Germany, it is recommended that perioperative intravenous fluid therapy should not necessarily be performed in children with short fasting times beyond neonatal age undergoing short (<1 h) and nonbleeding procedures [1▪▪]. In summary, the perioperative comfort and homeostasis of the children should be improved by optimized fasting times and liberal clear fluid intake until 1 h [38], and as a consequence a fluid therapy is often not really necessary in patients scheduled for short and nonbleeding procedures.

PERIOPERATIVE FLUID MANAGEMENT IN NEONATES

On the basis of tradition, the perioperative use of hypotonic electrolyte or electrolyte-free glucose-containing solutions is still common during neonatal surgery. Furthermore, in the neonatal age group, the combined effects of perioperative hypotonic fluids and ADH on water reabsorption in the kidney may lead to a decrease in plasma sodium concentration [39]. In accordance with this, Edjo Nkilly *et al.* [40] found that the calculated free water intake correlated with the decrease in sodium concentration during neonatal surgery. The authors concluded that the routine use of hypotonic electrolyte solutions during neonatal surgery should be questioned. In another

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observational study, the intraoperative infusion of 10 ml/kg/h of a balanced isotonic electrolyte solution with glucose 1% was associated with stable sodium and glucose concentrations in neonates [41]. Datta *et al.* compared the effects of an intraoperative infusion of 10 ml/kg/h of glucose 1% and 2% in Ringer's lactate in neonates with a low body weight of 1.6–2.8 kg. The authors found that the studied solutions were equally effective in maintaining glucose homeostasis but that the glucose solution with a higher concentration inhibited catabolism, insulin resistance, rebound hyperglycaemia and acidosis [42▪]. Unfortunately, no marketing authorization for a balanced isotonic electrolyte solution with glucose 2% is presently available, but adding 6 ml glucose 40% to a 250-ml container will increase the glucose concentration by 1% [1▪▪]. Special care must be taken when administering electrolyte-free concentrated glucose solution: accidental hyperinfusion may result in deleterious incidents, for example, hyperosmolar hyperglycaemic coma [30▪].

SALINE 0.9% AND HYPERCHLORAEMIC ACIDOSIS

Saline 0.9% is still widely used because of its relatively safe profile and its low cost [7]. It avoids the risk of hyponatraemia, but it contains too much chloride and no bicarbonate precursor (Table 1). Infusion of high volumes may cause chloride overload leading to a suppression of renal blood flow and the renin–aldosterone system and hyperchloraemic acidosis [43]. In an animal study with accidental hyperinfusion, hyperchloraemic acidosis developed with saline 0.9%, whereas the acid–base parameters remained more stable with a balanced isotonic electrolyte solution [44]. Clinical studies including children undergoing major paediatric surgery and neurosurgery showed similar results [45▪,46]. With the concept of homeostasis in mind, the composition of saline 0.9% is definitely unphysiological, and balanced isotonic electrolyte solutions should be preferred because of their resemblance to extracellular fluid.

POSTOPERATIVE MANAGEMENT

Furthermore, short fasting times and early drinking as wanted by the children should be favoured also postoperatively [47]. For maintenance infusions in postoperative or nonsurgical patients, randomized clinical studies and meta-analyses showed a lower incidence of hyponatraemia when using isotonic instead of hypotonic electrolyte solutions with glucose 5% (e.g. [48▪▪,49]). In line with the above considerations, the American Academy of Pediatrics recommends in a recently published guideline that patients 28 days to 18 years of age requiring maintenance intravenous fluids should receive isotonic solutions with appropriate potassium chloride and dextrose as they significantly decrease the risk of developing hyponatraemia (evidence quality: A; recommendation strength: strong) [50▪].

Table 4. Perioperative fluid management in children

	Solution for infusion	Initial/repeated dose
Background infusion	BS-G[a]	10 ml/kg/h
Fluid therapy	BS[b]	×10–20 ml/kg
Volume therapy	Albumin, gelatine, HES[c]	×5–10 ml/kg
Transfusion	RBC[d], FFP[e], PT[f]	×10 ml/kg

Rule of 10s; adapted from [1▪▪].
[a]Balanced isotonic electrolyte solution with 1-2% glucose.
[b]Balanced isotonic electrolyte solution.
[c]Hydroxyethyl starch.
[d]Red blood cells.
[e]Fresh frozen plasma.
[f]Platelets.

CONCLUSION

A perioperative fluid management in children should be based on physiology and focused on the maintenance of the patient's homeostasis. Optimized preoperative and postoperative fasting times are important to avoid patient discomfort, iatrogenic dehydration and catabolic state. Balanced isotonic electrolyte solutions are recommended for fluid replacement in all age groups to avoid both hyponatraemia and hyperchloraemic acidosis. For intraoperative maintenance infusion, addition of

Table 5. Proposal for perioperative fluid management in children

Preoperative	Keep fasting times short (clear fluids up to 1 h preop.)
Minor procedures	Background infusion 10 ml/kg/h BS-G[a]
Intermediate procedures	Adjust background infusion to actual requirements during the course of the procedure Plus: BS[b] if additional fluid is required Plus: colloids[c] if additional BS is not sufficiently effective
Major procedures	Same as intermediate procedures Plus: blood products in case of critical haemodilution
Postoperative	Allow children to eat and drink soon after the procedure

Adapted from [1▪▪].
[a]Balanced isotonic electrolyte solution with 1–2% glucose.
[b]Balanced isotonic electrolyte solution.
[c]For example, albumin, gelatine, hydroxyethyl starch.

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1–2% glucose is recommended to avoid hypoglycaemia, lipolysis or hyperglycaemia. Modified fluid gelatine or hydroxyethyl starch in balanced electrolyte solution can safely be used to quickly normalize blood volume in case of perioperative circulatory instability and blood loss. A safe, simple, practical and effective proposal for perioperative fluid management in children is presented in Tables 4 and 5 (adapted from [1▪▪]).

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Conflicts of interest

R.S. has received fees for lectures and funds for research from B.Braun, Melsungen, Germany. The remaining authors have no conflicts of interest.

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