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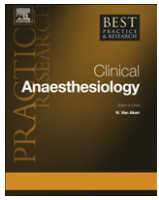

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Neonatal fluid management

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Perioperative fluid management in paediatrics has been the subject of many controversies in recent years, but fluid management in the neonatal period has not been considered in most reviews and guidelines.[1–3] The literature regarding neonatal fluid management mainly appears in the paediatric textbooks and few recent data are available, except for resuscitation and fluid loading during shock and major surgery. In the context of anaesthesia, many neonates requiring surgery within the first month of life have organ malformation and/or dysfunction. This article aims at reviewing basic physiological considerations important for neonatal fluid management and mainly focusses on fluid maintenance and replacement during surgery.

Physiological considerations: neonates are not just small adults

Major physiological changes occur within the first days and months of life. They mainly concern body composition, renal function and changes in the cardiovascular system.[4]

Body composition

Throughout foetal life and during the first 2 years of life the distribution of body fluid undergoes a gradual but significant change.[5] Total body water (TBW) represents as much as 80% of body weight in premature infants, 78% in full-term newborns and 65% in infants of 12 months of age compared to 60% in adults (Table 1). These age-related changes in TBW mainly reflect changes in extracellular fluid (ECF) with growth. As the body cells proliferate and organ development progresses, the ECF volume

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Table 1
Body composition and morphometric data in children (ICF: intracellular fluid; ECF: extracellular fluid).

	Premature	Full-term	1 yr	3 yr	9 yr	Adult
Body weight (BW kg)	1.5	3	10	15	30	70
Body surface area (BSA m^2)	0.15	0.2	0.5	0.6	1	1.7
BSA/BW	0.1	0.07	0.05	0.04	0.03	0.02
Total body water (% BW)	80	78	65	60		
ECF (% BW)	50	45	25	20		
ICF (% BW)	30	33	40	40		

decreases proportionally. It represents 50% of body weight in premature infants, 45% in full-term newborns and 25% in infants of 12 months of age compared to 20% in adults. The intracellular fluid compartment increases only moderately during the first year of life, representing 33% of body weight at birth and 40% of body weight by the end of the first year, and does not change substantially after that.

Renal maturation

Maturation of renal function is basically achieved by the end of the first month of life. Glomerular filtration increases rapidly from 34 weeks gestational age when kidneys have completed their nephronic structure.[6–8] After birth, renal vascular resistances decrease abruptly while systemic vascular resistances and arterial pressure increase. As a consequence, renal blood flow increases dramatically. This explains why glomerular filtration rate, still low during the first 24 h of life, rises very rapidly thereafter. During the first 6 weeks after birth, the area of cortical and juxtaglomerular nephrons, as well as the volume of glomerular capillaries and the size of glomerular membrane pores also increase. Tubular function is less mature than glomerular function at birth. Renal threshold for glucose is low explaining the high incidence of glycosuria even after moderate hyperglycaemia. The tubular capacity to reabsorb sodium is low in premature infants.[9] At term, the neonatal nephron begins to reabsorb sodium more actively in response to growth requirements. Sodium excretion in response to parenteral sodium load is also reduced. Careful control of sodium balance is essential in premature surgical neonates, as both hypernatraemia and hyponatraemia may have detrimental effects on the brain.

At birth, the newborn is unable to effectively concentrate urine. Clearance of free water is lower than that of adults thus explaining the impaired ability of newborn infants to cope with excessive water loading or water deprivation.

Finally, the renin–angiotensin–aldosterone system is functional in neonates[10] but feedback mechanisms are immature, especially in premature infants.[11]

Developmental cardiovascular changes

Newborns and premature infants have limited cardiovascular reserves in response to increased preload or afterload.[12–14] Any reduction in preload is also poorly tolerated owing to reduced compliance of the right ventricle and is rapidly followed by a reduction of systolic ejection volume. Cardiac output is high to compensate for the high oxygen affinity of foetal haemoglobin and to match the high oxygen consumption.[15] Cardiac output is highly dependent on heart rate in the neonatal period.[13] However, by the end of the first month of life, the capacity of the cardiovascular system to adapt is close to that of adults. In premature infants, excess of fluid will promote the persistence of patent ductus arteriosus.[16,17]

Maintenance requirements

Calorie requirement

The metabolic rate of a full-term newborn in a neutral environment is 32 kcal kg^{-1} per day during the first hours of life. Requirements increase rapidly during the first week of life, and then at a slower rate, increasing linearly with growth.[18]

In 1957, Holliday and Segar[19] estimated metabolic requirements for children at bed rest, and this estimation is still used in daily practice. The calculated calorie expenditure was 100 kcal kg^{-1} for infants weighing 3–10 kg, (1000 + 50) kcal kg^{-1} for each kilogram more for children between 10 and 20 kg, and 1 (500 + 20) kcal kg^{-1} for each kilogram over 20 kg. Half of those calories were thought to be required for basic metabolic needs and the remainder for growth. General anaesthesia essentially mimics calorie requirements at closer to basal metabolic rate.[20] As the maintenance needs for water paralleled energy metabolism, the estimated caloric expenditure was used to determine the maintenance fluid therapy (known as the 4–2–1 rule). Since the publication of this article, hypotonic solutions have had widespread use for decades until the danger of induced hyponatraemia was demonstrated in clinical practice.[21–25]

Water requirement

Under normal conditions, 1 ml of water is required to metabolise 1 kcal. This takes into account insensible water losses across the skin and respiratory tract, and urinary water loss. Therefore, in the awake child, calorie and water consumption are considered equal (Table 2). In anaesthetised children, Lindahl[20] calculated that 166 ml of water were required to metabolise 100 calories. Using indirect calorimetry, he calculated hourly maintenance fluid to be equal to the following expression 2.5× kg + 10 (ml h^{-1}). In term neonates, water intake is progressively increased during the first days of life from 60 ml kg^{-1} per day the first day and subsequently increased by 20 ml kg^{-1} per day to achieve 150 ml kg^{-1} per day at the end of the first week of life. Insensible water loss increases with decreasing body weight in premature infants, especially when they are cared under radiant warmer.[26] Several factors contribute to this large insensible water loss in premature infants: small size, an increased body-surface-area-to-body-weight ratio, increased thermal conductance, thinner more permeable and vascularised skin and a higher respiratory rate.

Electrolytes requirements

Daily sodium and potassium requirements were calculated by Holliday and Segar from the amount of electrolyte delivered by the same volume of human milk.[19] The daily needs were 3 mmol kg^{-1} per day sodium and 1–2 mmol kg^{-1} per day potassium. The combination of maintenance-fluid and electrolyte requirements results in a hypotonic electrolyte solution (0.2% saline equivalent). In premature infants, sodium and potassium requirements are higher than later in life, 3–5 mmol kg^{-1} per day for sodium and 2–4 mmol kg^{-1} per day for potassium mainly because of the immaturity of renal tubular function. Calcium requirements range between 0.8 and 1 mmol kg^{-1} per day.

Preoperative assessment

The preoperative assessment of fluid volume and state of hydration varies from elective surgery patients with no or slowly developing fluid deficit such as those scheduled for hernia repair to the severely sick premature infant with necrotising enterocolitis who is undergoing a dynamic deficit in blood and interstitial volume and in whom it is more difficult to evaluate fluid balance.

Vascular volume

The ultimate goal of perioperative fluid therapy is to maintain a correct fluid and electrolyte balance and, as a consequence, normal cardiovascular stability.[27] Indeed, dehydration and some medical conditions associated with third-space sequestration of fluids (e.g., intestinal occlusion) will in turn

Table 2
Fasting guidelines for elective surgery in neonates.

Ingested material	Minimum fasting period (h)
Clear liquids	2
Breast milk	4
Infant formula	4

affect vascular fluid volume. Restoration of an adequate vascular fluid volume is essential to maintain cardiovascular stability, organ perfusion and adequate tissue oxygenation. Isotonic transfer of fluid from the extracellular compartment to a non-functional interstitial space forms third-space volume. Replacement of intravascular volume loss should be performed by administration of normotonic and normo-osmolar solution. Crystalloid solutions such as Ringer lactate or normal saline, or even a colloid solution such as albumin can be used (see below). The prognosis of some medical conditions such as septic shock depends on the quantity and the rapidity of vascular loading; the younger the child, the greater the quantity of fluid loading related to body weight.[28–30] The fluid challenge is usually 10–20 ml kg^{-1} in children, but no clear recommendations can be found in the literature for the neonatal period even in the most recent published guidelines.[31]

Preoperative management of pyloric stenosis is much more codified. Pyloric stenosis is a medical emergency and not a surgical emergency. Preoperative correction of fluid and electrolyte deficits may require several hours or even days. The targets of preoperative fluid management is to correct dehydration and to obtain serum chloride $\geq$106 mmol l^{-1}, serum Na^+ $\geq$135 mmol l^{-1}, serum bicarbonate (HCO_3^-) $\leq$26 mmol l^{-1}, urine chloride (Cl^-) >20 mmol l^{-1} and urine output >1 ml kg^{-1} per hour. The most severe cases usually require an initial fluid challenge of 20 ml kg^{-1} of crystalloids to restore vascular fluid volume.

Fasting guidelines

There is now a large body of evidence that free intake of clear fluids up to 2 h preoperatively does not affect the pH or volume of gastric contents at induction of anaesthesia in children. While there have been relatively few studies in infants, these suggest that infants may be allowed clear fluids up to 2 h and breast milk 4 h preoperatively.[32,33] It was demonstrated >25 years ago that the gastric emptying of 110–200 ml of human milk was 82 ± 11% after 2 h in neonates and infants of <1 year of age, 84 ± 21% after whey-hydrosylated formula, 74 ± 19% after whey-predominant formula, 61 ± 17% after casein-predominant formula and 45 ± 19% after cow's milk.[34] Thus human milk and whey-predominant formula emptied faster than casein-predominant formula and cow's milk. Two other studies performed prior to anaesthesia demonstrated also that breast milk empties from the stomach faster than most formulas in infants and both require more than 2 h to ensure complete gastric emptying.[32,33] According to these data, the American guidelines recommended 4 h fasting time for breast milk and 6 h for infant formula and non-human milk.[35] These recommendations were also endorsed by The Royal College of Nursing that considered that there was insufficient evidence to change contemporary best practice (i.e., breast milk up to 4 h and formula and cows' milk up to 6 h).[36] However, recent Scandinavian guidelines recommended 4-h fasting for breast milk but also for formula milk in infants of <6 months of age.[37] Thus, it may be recommended to stop breast feeding and infant formula 4 h prior to anaesthesia in neonates (Table 2). This is our practice for otherwise healthy surgical neonates.

Intra-operative fluid management

Quantity of intra-operative fluids

Intra-operative fluid therapy is aimed at providing basal metabolic requirements (e.g., maintenance fluids), compensating for the preoperative fasting deficit and replacing losses from the surgical field.

When following modern more liberal nil per os (NPO) guidelines, fasting fluid deficit is expected to be minimal even in small infants and the sicker babies usually already have a functional intravenous line placed prior to surgery, and thus are expected to be correctly hydrated. Third-space losses may vary from 1 ml kg^{-1} per hour for a minor surgical procedure to as much as 15–20 ml kg^{-1} per hour for major abdominal procedures, or even up to 50 ml kg^{-1} per hour for surgery of necrotising enterocolitis in premature infants. Blood losses are replaced with either 1:1 ratio of blood or colloid, or 3:1 ratio for crystalloid. Third-space losses should be replaced with crystalloid (e.g., normal saline or Ringer lactate), but maintenance fluids are basically hypotonic as discussed above. Thus, intra-operative fluid administration requires two different types of fluids administered at different rates: one with maintenance fluids at a set rate (Table 2) and the other for replacement fluids.

Glucose: necessary or harmful?

The next question is whether or not administration of dextrose is necessary during surgery. In the last several years, there has been a complete re-evaluation of the place of glucose in routine intra-operative solutions. As already discussed above, energy requirements during anaesthesia are close to the basal metabolic rate. Administration of dextrose was previously deemed mandatory in children to avoid perioperative hypoglycaemia which may be difficult to diagnose in an anaesthetised child, but the risk of hyperglycaemia was, at that time, underestimated.

The risk of hypoglycaemia is a legitimate concern in neonates and small infants, especially in those on total parenteral nutrition. There is, however, no agreement in the literature regarding the definition of hypoglycaemia.[38] The value of 2.4 mmol l^{-1} is often proposed as the acceptable level in infants and children. In neonates, hypoglycaemia during fasting or illness is well known and results from several factors.[39] Whole-body glucose metabolism corrected for body mass in neonates is up to twice as high as in adults. Hepatic glycogen stores corrected for body mass are less in neonates than in adults. Gluconeogenic enzymes to convert amino acids to glucose are also inefficient. Prior to cardiopulmonary bypass, the incidence of hypoglycaemia is as high as 9% in neonates receiving glucose-free solutions.[40] In 1990, Larsson et al.[41] studied blood glucose concentrations in neonates undergoing major surgery during the first week of life. Intra-operative blood glucose levels were maintained by most neonates who did not receive intra- and preoperative glucose. However, hypoglycaemia occurred when a preoperative glucose infusion was interrupted during surgery or in neonates younger than 48 h of age.

Prolonged and severe hypoglycaemia is associated with extensive and widespread neuronal injury involving predominantly gray matter structures.[42,43] However, transient hypoglycaemia has also been associated with neurologic injury in neonates.[44,45] Thus, in neonates, preventing hypoglycaemia is essential, especially in asphyxiated neonates and those undergoing cardiac surgery.[39] Certain neonates are at increased risk of hypoglycaemia such as infants of diabetic mothers and those with the Wiedemann–Beckwith syndrome.

The danger of hyperglycaemia in the perioperative period is a real clinical issue that has been extensively reviewed.[46–48] Hyperglycaemia can induce osmotic diuresis and, consequently, dehydration and electrolyte disturbances. In the early 1980s, animal studies in adult animals clearly demonstrated that glucose worsens outcome from both global and focal ischaemia. The proposed mechanism of this injury is that, in the presence of an ischaemic or hypoxic insult, oxidative metabolism of glucose fails, and glycolysis, with its end-product of lactate, increases. With sufficient intracellular lactate accumulation, intracellular pH falls, which may lead to compromised cellular function or cell death.

In contrast to the adult, moderate hyperglycaemia in the neonate seems to protect the brain from ischaemic damage.[39] Indeed, hyperglycaemia increases cerebral high-energy reserves and glycogen stores.[49–52] Glucose uptake and metabolism is slower and lactate accumulates slower in the neonatal brain compared with the adult brain. Finally, lactate clearance is enhanced, thereby avoiding the toxicity of lactacidosis. In young infants, glucose infusion at a rate of 120 mg kg^{-1} per hour is sufficient to maintain an acceptable blood glucose level and to prevent lipid mobilisation.[53,54]

Clinical guidelines

To avoid both hyper- and hypoglycaemia in the neonates, usually two distinct intravenous lines are useful: one for providing glucose and metabolic requirements, the second for fluid replacement. Our practice is to use polyionique B66 (balanced isotonic hydrating solution containing sodium chloride (NaCl)120 mmol l^{-1} plus 0.9% dextrose) for maintenance fluid therapy and replacement of most of third-space-compartment losses and to monitor closely blood glucose levels during surgery.[55] As the volume of fluid administered is usually quite large, the amount of glucose is sufficient to avoid hypoglycaemia and usually does not induce hyperglycaemia. A glucose-infusion rate between 120 and 250 mg kg^{-1} per hour is sufficient to avoid hypoglycaemia and to prevent lipid mobilisation in neonates and infants.[56] In paediatric cardiac surgery, glucose administration decreases the incidence of hypoglycaemia, without significantly affecting the incidence of hyperglycaemia. Moderate intra-operative glucose administration (150 mg kg^{-1} per hour) may be recommended to achieve this goal.[57,58]

Volume replacement during infancy: indications and choice of crystalloids and colloids

Crystalloids (e.g., normal saline or Ringer lactate) are first administered to treat absolute or relative blood-volume deficits frequently observed during surgery in children. Their advantages include their low cost, their lack of effect on coagulation, the absence of risk of anaphylactic reaction and of risk of transmission of any known or unknown infectious agent. This practice should also apply to premature and newborn infants. Indeed, studies performed in hypotensive premature infants or polycythaemic newborns have demonstrated that normal saline is as effective as albumin to restore and maintain arterial pressure or to treat neonatal polycythaemia.[59–62] In addition, in premature infants, crystalloid administration was causing less fluid retention in the first 48 h than 5% albumin. However, volume replacement with crystalloids in neonates on veno-arterial membrane oxygenation aggravated the oedema in a pre-existing situation of capillary-leakage syndrome, whereas volume replacement with colloids had lesser effects on oedema.[63]

The rate of fluid administration will be indicated by the cardiovascular condition. Normally, 15–20 ml kg^{-1} of Ringer lactate solution over 15–20 min will re-establish cardiovascular stability. After administration of a total of 30–50 ml kg^{-1} of crystalloid solution, the administration of a colloid solution (albumin or synthetic colloid) to maintain intravascular osmotic pressure is indicated.[64]

Hydroxyethylstarch (HES) preparations are becoming very popular for vascular loading in adults and children.[65] However, the number of paediatric studies aimed at evaluating HES efficacy and tolerance is limited and, within years, available HES solutions have changed with reduced molecular weight and molar substitution ratio. The third generation of HES (130/0.4) has reduced adverse effects on coagulation and renal function than older solutions while maintaining efficacy.[66] Only studies performed with this third-generation HES (130/0.4) are discussed, as HES of first and second generations are no longer available in most countries. The European prospective multicentre observational post-authorisation safety study enrolled 300 paediatric patients who received a third-generation HES.[67] Among the paediatric patients, ~10% were neonates. Whatever the age group, no serious adverse event were reported while the mean volume infused was 11 ± 4.8 ml kg^{-1}. However, only children with normal renal function and intact coagulation system were included in this prospective study. Chong Sung et al.[68] showed that the administration of 10 ml kg^{-1} HES 130/0.4 to children undergoing cardiac surgery does not cause more bleeding or a higher transfusion requirement than fresh frozen plasma, but no neonates were included in this randomised clinical trial. Using a higher infusion volume of 15 ml kg^{-1}, Haas et al.[69] found that activated modified thromboelastography values were significantly more impaired after HES 130/0.4 than after albumin or gelatine in children with weight range of 3–15 kg. They concluded that, from a haemostatic point of view, it might be preferable to use gelatine solutions as an alternative to albumin rather than HES 130/0.4. The most recent study randomised 119 children to receive 50 ml kg^{-1} of either 4% albumin or 6% HES 130/0.4 for intra-operative fluid-loading replacement in children undergoing cardiac surgery.[70] They found similar blood loss between the two groups but a higher number of children in the albumin group required allogenic transfusion whereas intra-operative fluid balance was lower in the HES group. Although many infants were enrolled in this study, neonates (<28 days) were excluded. To summarise, the new generation of HES seems to be safer than the older generation, but sufficient safety data are lacking to recommend its use in neonates owing to their immature renal and coagulation functions.

Gelatines have been used for many years in children but also in early infancy to treat intravascular fluid deficits. Haemaccel™ is no longer used in many countries owing to its high risk of anaphylactic reaction. Haemaccel™ was demonstrated to be as effective as 4.5% albumin to maintain blood pressure during major surgery in neonates, but less effective to maintain plasma colloid osmotic pressure and plasma albumin concentration.[71]

Although the use of albumin has been challenged owing to its high cost and to its uncertain risk of transmission of non-conventional agents, it remains the main colloid used in the neonatal period and early infancy for volume expansion.[72,73] In hypotensive premature infants, 4.5% albumin was demonstrated to be as effective as fresh frozen plasma to restore blood pressure, but more effective than 20% albumin.[74] This suggests that the volume of albumin administered is more important that its concentration to maintain or restore cardiovascular stability. Thus, 5% albumin is still the preferred

Table 3
Transfusion thresholds for infants under 4 months of age.

Anaemia in the first 24 h	Haemoglobin 12 g/dl (Hct ~ 0.36)
Neonates receiving intensive care	Haemoglobin 12 g/dl
Chronic oxygen dependency	Haemoglobin 11 g/dl
Late anaemia, stable patients	Haemoglobin 7 g/dl
Acute blood loss	10% of blood volume

colloid in newborn infants as it is iso-oncotic to plasma and very effective to maintain blood pressure and plasma colloid perfusion pressure.[71]

The use of fresh frozen plasma should be restricted to neonates and children with proven coagulation disorders.

Guidelines for neonatal blood transfusion

Blood-transfusion safety has dramatically improved in recent years, but unnecessary transfusion still carries some risks that justify reasonable indication prior to administering blood products. The clinical indication for the administration of erythrocytes to a patient during the course of surgery should be dictated only by the necessity to maintain oxygen-carrying capacity and oxygen delivery to peripheral tissues.

Appropriate transfusion thresholds for the first 4 months of age are higher than for older children due to physiological differences between this age group and adults. Indeed, neonates and infants have higher oxygen consumption per kilogram and a higher cardiac-output-to-blood-volume ratio than adults. Normal haemoglobin values are significantly higher at birth and decrease gradually over the first few months of life. In addition, at birth, foetal haemoglobin is the main haemoglobin and has a higher affinity for oxygen than adult haemoglobin. Suggested transfusion threshold according to clinical status and haemoglobin levels have been published for infants of <4 months of age[75] and are summarised on Table 3. These were not published with special reference to the surgical patient.

Accurate monitoring of blood loss in neonates is vital to any replacement regimen. It can be achieved by weighing sponges and observing small, calibrated, suction bottles but visual estimation is also essential in the practice of neonatal anaesthesia. The concept of measuring *a priori* the allowable red cell loss based on the starting blood volume, haemoglobin and haematocrit combined with proper cardiovascular monitoring (e.g., heart rate, blood pressure and urine output) and haemoglobin measurements may help to guide blood replacement.

Blood-volume estimates are based on the age of the patient. The estimated blood volume (EBV) is 90–100 ml kg^{-1} in premature infants, 80–90 ml kg^{-1} in term neonates and then decreases to achieve 70–75 ml kg^{-1} in infants >3 months of age. EBV should be calculated and indicated on anaesthesia chart when haemorrhagic surgery is performed. Allowable blood loss (ABL) is calculated as follows:

$$ABL = weight \times EBV \times \left[\frac{(H_o - H_1)}{H_{mean}}\right]$$

where H_o = initial haematocrit, H_1 = target haematocrit and H_{mean} is the average haematocrit.

Losses below the maximum allowable can be replaced with crystalloids or colloids as discussed previously. In the absence of ongoing blood loss, ~4 ml kg^{-1} of packed red cells will be required to raise the haemoglobin level by 1 g dl^{-1}.

Conclusion

Neonates are not small adults. The large extracellular space explains why the amount of fluid required to maintain or to restore blood volume is considerably higher in neonates compared to older children and adults. Avoiding hypoglycaemia is essential in the neonatal period. The rationale for fluid loading and blood transfusion is, however, close to that recommended in adults.

Practice points

- The ECF compartment represents 45% of body weight in full-term neonates explaining why large volumes of isotonic fluids may be required during major surgery associated with intravascular volume depletion
- Both hypoglycaemia and hyperglycaemia have to be avoided. In young infants, glucose infusion at a rate of 120 mg kg^{-1} per hour is sufficient to maintain an acceptable blood glucose level and to prevent lipid mobilisation
- Blood glucose levels should be closely monitored during surgery
- The new generation of hydroxyethylstarch preparation seems to be safer than the older generation preparation, but sufficient safety data are lacking to recommend its use in neonates owing to their immature renal and coagulation functions
- 5% albumin is the preferred colloid in newborn infants as it is iso-oncotic to plasma and very effective to maintain blood pressure and plasma colloid perfusion pressure
- In the absence of ongoing blood loss, ~4 ml kg^{-1} of packed red cells will be required to raise the haemoglobin level by ~1 g dl^{-1} in neonates

Research agenda

- Short- and long-term safety data after administration of hydroxyethylstarches in the neonatal period
- The paradoxical neuroprotection associated with moderate hyperglycaemia in newborn infants
- Non-invasive monitoring of vascular volume in newborn infants

Conflict of interest statement

None declared.

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