Hyperglycaemia, hyponatremia and volume overload(2,18).

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The situation is different in newborns. They need 4-8 mg/kg/min (approximately 300 mg/kg/hr) of glucose for sustaining brain development(2), deprivation of which may adversely affect neuro-developmental outcome(3,4). Neonates are susceptible to develop hypoglycaemia due to low glycojen reserves. Hence they need glucose as a part of their maintenance fluid during surgery. However, how much glucose neonates require during surgery still open to debate. Hyperglycaemia too may be detrimental to neonates. Adverse clinical outcomes associated with neonatal hyperglycaemia include intraventricular haemorrhage, retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia, osmotic diuresis, impaired immunity, delayed wound healing, renal injury and neuronal lactic acidosis(5-14).

Neonates are capable of mounting substantial neuro-endocrine response to both surgical stress and decreased glucose supply. This manifests as a rise in cortisol, glucagon, catecholamines and vasopressin, along with fall in insulin. The result is a rise in blood glucose concentration through gluconeogenesis, fat mobilisation and protein catabolism(15,16,17). However, such compensation occurs at the expense of valuable energy reserves, namely glycogen, fat and proteins.

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Key words: glucose, dextrose, neonate, children, fluid and surgery

Introduction

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NEONATAL EUGLYCEMIC RANGE

There has been considerable debate about the threshold of neonatal hypoglycaemia. It was commonly believed that neonates can tolerate episodes of asymptomatic moderate hypoglycaemia. However, Lucas et al (1985)3 demonstrated neurodevelopmental impairment in infants with recurrent episodes of asymptomatic moderate hypoglycaemia (blood glucose < 2.6mmol/L). Koh et al (1985)4 also demonstrated abnormal sensory evoked potentials in children with blood glucose less than 2.6mmol/L. Subsequently WHO designated a blood glucose “operational threshold”(19,20) of less than or equal to 2.6mmol/L (45mg/dL) as requiring treatment in neonates, both term and pre-term.

On the other hand, the threshold for significant neonatal hyperglycaemia is unclear. Various studies have reported adverse outcomes at blood glucose level greater than 8.3mmol/L (150mg/dL) (5-8). More severe outcomes were reported with prolonged hyperglycaemia.

NEONATAL RESPONSE TO SURGICAL & METABOLIC STRESS

Neonatal response to anaesthesia and surgical stress has been extensively studied. Anand et al(15-17) observed that the neonates are capable of mounting a substantial endocrine and metabolic response to surgical stress, the main features of which are an increase in plasma epinephrine, nor-epinephrine, cortisol, glucagon and beta-endorphin levels; a fall in nor-epinephrine, cortisol, glucagon and beta-endorphin levels; a fall in plasma epinephrine, nor-epinephrine, cortisol, glucagon and beta-endorphin levels; a fall in plasma insulin: glucagon ratio; and accompanying hyperglycaemia and hyperlactatemia. Their research revealed that neonates develop significant perioperative hyperglycaemia, the level of which correlates strongly with plasma glucagon and epinephrine levels. This is accompanied by rise in plasma insulin: glucagon ratio; and accompanying hyperglycaemia and hyperlactatemia. Their research revealed that neonates develop significant perioperative hyperglycaemia, the level of which correlates strongly with plasma glucagon and epinephrine levels. This is accompanied by rise in free fatty acids (FFA) and ketone bodies (KB). The insulin: glucagon ratio is significantly reduced at the end of surgery. Thus they concluded that stress related hormonal changes in preterm and term neonates may precipitate a catabolic state characterised by glycoegenolysis, gluconeogenesis, lipolysis and mobilisation of gluconeogenic substrates in the immediate post-operative period. A higher intra-operative stress response was associated with a higher post-operative mortality and poorer prognosis.
Glucose deprivation or restriction during surgery may amount to metabolic stress in a neonate prompting a brisk metabolic response. The response of young infants to fasting has been described by Leon et al(21) as a sequence starting with an initial fall in blood glucose followed by a fall in the concentration of gluconeogenic substrates (lactate and alanine). There after occurs a rise in free fatty acids (FFA) as lipolysis is initiated, followed by a brisk rise in beta-hydroxy butyrate (3-HOB) as hepatic ketogenesis starts(26) and a resultant alteration in biochemical parameters including a fall in pH, base excess and bicarbonate, and rise in anion gap (high anion gap metabolic acidosis). These changes are brought about by a fall in plasma insulin level followed by a rise in plasma glucagon, epinephrine and growth hormone.

NEED FOR PERI-OPERATIVE GLUCOSE

Fujino et al(22) and Yamasaki et al(23) have observed that intra-operative glucose supplementation reduces ketogenesis, attenuates post-operative insulin resistance and suppresses protein catabolism in adults. However, the role of intra-operative glucose supplementation in neonates is still controversial and there is no consensus yet as to the amount of glucose that is optimal for neonates during surgery.

Various studies have investigated the effect of different glucose containing fluids in paediatric populations during surgery. PubMed was searched with the following key words: glucose, dextrose, neonate, children, fluid and surgery. The results were scanned and studies that dealt with intra-operative glycemic control in children were selected for discussion. Their findings, with respect to various metabolic and biochemical parameters, have been summarized below.

Glucose homeostasis

A rise in blood glucose was observed in most neonates undergoing, even with the intra-operative use of plain Ringer acetate (RA) (24,25). Among studies in older infants and children, although net rise in blood glucose was observed with the use of plain Ringer lactate (RL) during surgery(27-30), fall in blood glucose was noted in isolated cases with the use of dextrose free fluids.(27,28)

Sumpelmann(31) et al used 1% dextrose containing isotonic balanced salt solution in neonates undergoing major surgeries at a mean infusion rate of 10ml/kg/min. Blood glucose was maintained in the normoglycaemic range and there was no incidence of hypoglycaemia or hyperglycaemia with the use of this regimen. Studies on the effect of 1% dextrose containing intra-operative fluid in older infants and children have demonstrated a net rise in blood glucose during surgery,(27,28,30) which returned to normal by one hour after surgery(30).

The use of 2-2.5% dextrose containing fluids during surgery in paediatric patients has been shown to cause a rise in blood glucose.(24,28,29,30,32,33) The rise was significantly greater with 2.5% dextrose in RL as compared to 1% dextrose in RL.(30)

The use of 5% dextrose containing fluid during surgery in paediatric patients have invariably produced hyperglycaemia.(27,29,33) Larsson et al(25) and Sandstrom et al(26) have studied the effect of continuing 10% dextrose at standard maintenance rate during surgery in neonates, with additional losses being replaced with plain Ringer acetate. Both studies reported a rise in blood glucose at the end of surgery which remained significantly elevated above baseline even 8 hours after surgery. (26) The rise in blood glucose is explained by the metabolic and endocrine response of the children to surgical stress resulting in an increase in counter-regulatory hormones, mainly epinephrine and glucagon, as described by Anand et al(18,19).

A fall in blood glucose was observed in patients who received glucose containing fluids in the pre-operative period and were subsequently switched to glucose free fluid during surgery. With intra-operative dextrose supplementation, blood glucose level was maintained in these patients.(25,26)

Electrolyte balance

Post-operative hyponatremia is a major concern in neonates with the use of hypotonic fluids during surgery. Dubois et al(30) and Hongnat et al(32) found hyponatremia during the post-operative period using hypotonic fluids.

Dubois et al compared RL (Na+ = 130 mmol/L) to a combination of RL & D5 (resultant Na+ 65 mmol/L) in children aged 3 months to 10 years and found that serum sodium concentration is maintained in patients receiving RL compared to patients receiving the combination of RL and D5 who show a fall in serum sodium.

Hongnat et al(32) compared two fluids, one having 46 mmol/L and the other 62 mmol/L sodium in children aged 3 months to 10 years. They observed a fall in serum sodium concentration at the end of surgery in both groups, the change being greater in the group receiving the fluid with the lower concentration of sodium.

Sumpelmann et al(31) used isotonic balanced salt solution with 140 mmol/L sodium in neonates. No change in serum sodium concentration was reported in the post-operative period with the use of this fluid.

In a recent study Edjo Nkilly et al(34) observed cases with dilutional hyponatremia following the intraoperative use of hypotonic solutions in neonates. They concluded that intra-operative i.e. free water administration of more than 6.5 ml/kg/hr resulted in a significant fall in serum sodium.

Acid-Base Status

Studies that scrutinised the effect of intra-operative dextrose supplementation on acid-base balance yielded conflicting results. Nishina et al(33) reported a fall in pH and BE at the end of surgery in infants receiving dextrose free solution during surgery, which they attributed to ketosis due to glucose deprivation. Sumpelmann et al(31) used 1% glucose containing solution in neonates and noted a statistically significant decrease in bicarbonate and base excess. However, the reported changes in both the parameters were clinically insignificant. On the contrary, Sandstrom et al(26) reported no change in pH during the use of dextrose free fluid during surgery in neonates. The change in pH may not have been evident due to the smaller sample size of their study.

Metabolic parameters

The effect of intra-operative glucose supplementation on the production of ketone bodies (KB) and free fatty acids (FFA) in paediatric patients has been studied. Mikawa et al(29) reported no change in the levels of KB and FFA in children aged 1.5 - 9 years with the use of dextrose free fluids. On the other hand, Sandstrom et al(26) and Nishina(33) et al observed a rise in KB and FFA in infants. There was no rise in KB and FFA in patients receiving glucose supplementation during surgery in any of the studies. The production of ketone bodies appears to be promoted by pre-operative fasting and intra-operative use of glucose free fluids, especially in infants.

Endocrine parameters

Mikawa et al. (29) observed insulin levels in patients aged 1.5 – 9 years and reported no significant difference at the end of surgery among those receiving plain RL and those receiving 2% or 5% dextrose in RL. On the other hand Nishina et al(33) reported a fall in insulin levels at the end of surgery in infants receiving plain RL, unlike those given 2% and 5% dextrose in RL during surgery. The difference in their findings can be attributed to the difference in age groups of the study populations. In a recent study comparing 1%, 2% and 4% dextrose containing solutions for intra-operative use in neonates(34), we observed that blood glucose increased in all three groups at the end of surgery, with no significant difference in blood glucose and incidence of hyperglycaemia among them. Base excess, bicarbonate, and pH showed a significant fall at the end of surgery in patients receiving 1% dextrose. Serum insulin was significantly lower and glucagon: insulin ratio higher in patients receiving 1% dextrose. At 24 hours after surgery, blood glucose and incidence of hyperglycaemia was significantly higher in patients receiving 1% dextrose. Thus, although 1% dextrose containing solution appears as effective as higher glucose concentrations in maintaining blood glucose level and preventing...
hypoglycaemia during surgery in neonates, there is evidence to suggest increased catabolism in these patients compared to those receiving glucose at a higher rate that is closer to the physiological requirement of glucose in neonates. No significant difference in glucose homeostasis, electrolyte balance, metabolic parameters and endocrine parameters were observed between neonates given 2% and 4% dextrose containing fluids.

Table 1. SUMMARY OF FINDINGS OF VARIOUS STUDIES COMPARING THE USE OF INTRA-OPERATIVE DEXTROSE CONTAINING FLUIDS IN PEDIATRIC PATIENTS.

<table>
<thead>
<tr>
<th>Study</th>
<th>Age group</th>
<th>No. of patients</th>
<th>Fluids compared</th>
<th>Parameters measured</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilsson et al (1984)</td>
<td>2w-22w</td>
<td>70</td>
<td>RA D2.5RA</td>
<td>BG</td>
<td>Pre-op BG independent of age, weight, duration of fasting. Increase in BG at end of surgery in both groups</td>
</tr>
<tr>
<td>Welborn et al (1986)</td>
<td>1m-6m</td>
<td>466</td>
<td>RL D5RL</td>
<td>BG</td>
<td>Asymptomatic hypoglycaemia during pre-operative fasting. Rise in blood glucose in both groups during surgery. Some patients receiving RL showed fall in BG. D5RL invariably cause hyperglycaemia.</td>
</tr>
<tr>
<td>Welborn et al (1987)</td>
<td>1m-6y</td>
<td>162</td>
<td>RL D2.5RL</td>
<td>BG</td>
<td>Rise in mean BG in all three groups at end of surgery. RL and D2.5RL showed fall in BG in individual cases. D2.5RL did not show fall in BG in any of the cases.</td>
</tr>
<tr>
<td>Larsson et al (1990)</td>
<td>0-7d</td>
<td>90</td>
<td>RA RA-D10</td>
<td>BG</td>
<td>Rise in BG in both groups during surgery. Fall in BG if pre-op glucose administration interrupted, more with plain RA.</td>
</tr>
<tr>
<td>Mikawa et al (1991)</td>
<td>1.5-9yrs</td>
<td>45</td>
<td>RL D2RL D3RL</td>
<td>BG, FFA, TG, KB, insulin</td>
<td>No group experienced hypoglycaemia. D3RL produced hyperglycaemia. Other parameters remained WNL.</td>
</tr>
<tr>
<td>Hongvat et al (1991)</td>
<td>3m-10y</td>
<td>68</td>
<td>D5 0.3S D2.5 0.4S</td>
<td>BG, Na+</td>
<td>7.4% incidence of hypoglycaemia during fasting. Rise in BG, fall in Na+ in both groups in post-operative period. Change greater in D5 0.3S. Change greater in children less than 4 yr age.</td>
</tr>
<tr>
<td>Dubois et al (1992)</td>
<td>3m-10y</td>
<td>79</td>
<td>RL RLD1 RLD2.5 (50%RL+ 50% D5)</td>
<td>BG, Total protein, Na+</td>
<td>BG rose in all groups, most in RLD2.5. Na+ decreased in RLD2.5. RLD1 most appropriate.</td>
</tr>
<tr>
<td>Sandstrom et al (1993)</td>
<td>0-6d</td>
<td>14</td>
<td>RA RA-D10</td>
<td>BG, FFA, 3-HOB, pH, Lactate, Pyruvate, TG, Alanine, Glycerol</td>
<td>BG rose in both. pH showed no difference. RA showed rise in FFA, β-HOB, fall in lactate.</td>
</tr>
</tbody>
</table>

RA = Ringer acetate, RL = Ringer lactate, D = Dextrose, BG = Blood glucose, KB = Ketone body, 3-HOB = Beta-hydroxy butyrate, FFA = Free fatty acid, TG = Triglyceride, BE = Base excess, AG = Anion gap, GL = Glucagon : Insulin

Keeping such evidence in view, the Association of Paediatric Anaesthetists of Great Britain and Ireland issued consensus guidelines (35) 2007 stating that maintenance fluid in term neonates should be 10% Dextrose at 2-3ml/kg/hr in the first 48hrs of life, followed by 10% Dextrose in N/5 Saline at 4ml/kg/hr from the third day of life onwards. Any fluid deficit or surgical loss should be corrected with isotonic fluids. Children who warrant glucose in their intraoperative fluids are neonates in their first 48hrs of life and children on dextrose containing fluids or parenteral nutrition pre-operatively. Children of LBW, prolonged surgery (>3hrs) or under extensive regional anaesthesia should have serial monitoring of blood glucose or should receive a 1-2.5% dextrose containing maintenance fluid.

The German Scientific Work Group for Paediatric Anaesthesia published the European Consensus Statement (36) in 2011 stating that intraoperative infusions in children should have an osmolality and sodium concentration close to the physiological range in order to avoid hyponatraemia , an addition of 1-2.5% glucose in order to avoid hypoglycaemia, lipolysis or hyperglycaemia, and should include metabolic anions (i.e. lactate, acetate or malate) as bicarbonate precursors to avoid acid–base disturbances.

CONCLUSION

Evidence suggests that neonates and infants need dextrose supplementation during surgery, albeit at a lower rate than their normal maintenance requirement. The interruption of glucose supply in children of this age group during the peri-operative period can result in hypoglycaemia, hypercatabolism, ketogenesis and delayed hyperglycaemia. The exact amount of dextrose needed in the peri-operative period is still under consideration. The rate at which glucose is being supplied depends both on the dextrose concentration of the maintenance fluid and the rate of infusion, and must be adjusted according to individual surgical needs. Although intra-operative dextrose supplementation in infants has demonstrated better biochemical and metabolic stability, definite benefit in terms of improvement in surgical outcomes is still to be proven and warrant larger trials. Till such time that further definitive evidence comes to light, the use of 1 – 2.5% dextrose containing isotonic fluids for intra-operative maintenance in neonates and infants appears to be most prudent.

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