7

Glucose Infusions into Peripheral Veins in Neonates with Hypoglycemia

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1. Introduction

Intravenous glucose infusions into peripheral veins are often needed, in addition to oral feedings, to elevate blood glucose levels in the management of neonatal hypoglycemia. Central venous catheters are rarely inserted, when the duration of such treatment is less than a few days. More than half of peripheral venous cannulations extravasate by 36 h, or even faster, if medication is administered concomitantly (Möller et al., 1996, Hecker et al., 1991). Complications, including local swelling and in the worst cases damage to tissue may occur. Intravenous solutions containing 10 or 15 percent glucose are most commonly used in hypoglycemic infants. A glucose concentration of 15% has generally been regarded as the highest acceptable for use in solutions infused into peripheral veins in neonates. (Kien, 1993). However, 10% and even 15% glucose infusions increase fluid load especially in patients, who need high glucose intakes to reach sufficient energy intake or to maintain normal plasma glucose levels. Although large fluid volumes of short duration are well tolerated in neonates (Leake, et al, 1976), the effect of continuous rapid infusions on the fluid clearance have not been determined. First voiding might be delayed due to elevated Arginine vasopressin levels in newborn infants delivered vaginally after a prolonged and stressful labor (Vuohelainen T et al., 2007 and 2008). A poor fluid tolerance during the first days of life can be anticipated and cautious fluid administration might be indicated especially in such infants.

Earlier studies suggest that the development of phlebitis does not depend so much on the osmolarity of the solution as other factors causing phlebitis, for example material of the catheter (Madan et al., 1992). Factors affecting the development of infusion phlebitis include vein characteristics, size and material of the catheter, duration of infusion and the osmolarity and pH of the infusion solution. Experimental infusions of 10% glucose with electrolytes (pH 4.93, osmolarity 727 mOsm/kg) into rabbit ear veins cause phlebitis by reason of its acidity and an infusion of amino acids (pH 6.29, osmolarity 929 mOsm/kg) by reason of its high osmolarity. On the other hand, admixture of these solutions causes only minor phlebitic changes and the fluid components eliminate each others' damaging effects on the tissue (Kuwahara et al., 1998a). In the same animal model, the tolerance of peripheral venous endothelial cells was for 8 h in 820 mOsm/kg, 12 h in 690 mOsm/kg and 24 h in 550 mOsm/kg solutions, respectively, suggesting that a planned volume of solutions with high osmolarity should be infused rapidly rather than slowly to avoid the development of phlebitis (Kuwahara et al. 1998b). In the management of hypoglycemia, however, only continuous

infusions can be used. In such occasions the effect of the infusion rate on the risk of phlebitis seems not have been established. Earlier surveys suggest that high infusion flow rates might even markedly increase the risk of infusion failure (Hecker 1989, Hecker, et al 1991).
The occurrence of phlebitis has been evaluated in adults in a comparison of peripheral infusions of nutrient solutions with and without 20% fat emulsion (Daly et al., 1985). Adding fat to the fluids did not protect the veins from the development of phlebitis. Infiltration was more dependent on the catheters than on the osmolarity of solutions. In keeping with this, peripheral intravenous nutrition caused phlebitis in all patients using Teflon cannulas, but in only 7% using silicone catheters. The risk of phlebitis was very low even when nutrition solutions of an osmolarity of 1250 mOsm/kg were administered via the latter catheters (Madan et al., 1992).
Glucose solutions are acid and hyperosmolar, the 15% solution pH ranging between 3.5–5.5 and osmolarity 832.5 mOsm/kg and the 20% solution 4.0 and 1110 mOsm/kg. In spite of this, the latter solution might be a better choice in the management of hypoglycemia, because the fluid administration rate of the 20% solution to reach the same glucose intake is 25% lower compared to 15% glucose solution. Thus, risk of excessive fluid load can be decreased by using 20% glucose instead of 15% glucose infusion. As far as we know no earlier studies comparing the infusions of 15 % and 20% glucose into peripheral veins of newborn infants have been done.
The purpose of our study was to evaluate, whether peripheral intravenous 20% glucose solutions are as well tolerated as 15% glucose solutions in the management of neonatal hypoglycemia.

2. Patients and methods

The study was undertaken in the neonatal unit of Tampere University Hospital (Vanhatalo and Tammela, 2010). Newborn infants with hypoglycemia for which initiation of intravenous glucose infusion was prescribed at the discretion of the attending physician, were included in the study if they fulfilled the following criteria: (1) birth weight of 2000 g or more, (2) no significant malformations diagnosed, (3) intensive care not needed, (4) written informed consent obtained from the parents. Infants in intensive care were excluded in order to minimize confounding factors, including need of vasoactive infusions and/or multiple intravenous medications.
Hypoglycemia was defined as a plasma glucose level below 2.6 mmol/L and hyperglycemia as above 7.7 mmol/L. All infants received either their own mother's or banked pooled breast milk. On-demand breast and/or bottle feeding was preferred. Breast-fed infants were weighed before and after feedings, in order to measure the ingested milk volume. The minimum cumulative amount of breast milk was 80 mL, divided by 8-10 feedings, in the first day of life. The cumulative milk volume was daily increased by 80 mL, up to 170 mL/kg/day. Increasing the daily number of oral feedings was the first treatment for hypoglycemia. Gavage feeding was used in babies, who were sucking poorly. Intravenous glucose infusion was started at the discretion of the attending physician in cases with symptomatic hypoglycemia, recurrent blood glucose levels below 2.6 mmol/L, in spite of increased oral or tube feedings, and in hypoglycemic infants, who tolerated poorly enteral feedings. The infants were randomized to receive either 20% (group 20%, 60 infants) or 15% (group 15%, 61 infants) peripheral intravenous glucose infusions at an initiation glucose intake rate of 8 mg/kg/min, i.e. 2.4 mL/kg/h in the group 20% and 3.2 mL/kg/h in the 15% group.

The group allocation of each patient was written in a sealed envelope, which was opened after the written consent was received from the parents. Because infusion rates were dependent on the glucose concentration the group allocation was not possible to be blinded.
The infants' plasma glucose levels were measured every 4 h and the infusion rate reduced after each measurement by 0.5 mL/kg/h at blood glucose levels between 3.5–4 mmol/L and by 1 mL/kg/h at blood glucose levels above 4 mmol/L. The infusion was stopped when the plasma glucose level was 3.5 mmol/L or higher at an infusion rate of 2 mL/h. Plasma glucose surveillance was continued, until levels had remained normal (more than 2.9 mmoL/L) for 24 h after discontinuation of the glucose infusion. When the cannulation site had to be changed, local signs of phlebitis at the previous site were scored from 0 to 3 using a modified Maddox scale (Maddox and Rush, 1977), by the attending physician. Cumulative severity, i.e. the sum of scores for phlebitis, was calculated during the infusion period. Number of cannulation site changes, duration of intravenous infusions and daily weights of the infants were recorded. Weight changes were calculated as percentages of birth weight. Preterm infants were born at less than 37 weeks' gestational ages. Infants with birth weight less than 2 SD from the mean for gestational age were defined as small for gestational age (SGA).

0 No pain around the tip of the catheter, no color, no redness, no hardening, vein not hard when palpated.
1+ Pain around the tip of the catheter and redness
2+ Pain around the tip of the catheter, redness and swelling
3+ Pain around the tip of the catheter, redness, swelling and hardening

Table 1. Modified Maddox score scale (Maddox and Rush, 1977): observation criteria for phlebitis.

2.1 Statistical analysis

Irritation in the site of infusion, number of cannula site changes and weight gain were chosen as primary end points. The sample size was calculated on the assumption that either glucose solution might reduce the mean number of cannula site changes from 1.5 to 1.0. With 80% power and statistical significance level below 0.05 the sample size would be 57 in each group. The dropout rate was estimated to be about 5%, and thus the goal was to recruit 60 infants for both groups.
t-test, Mann–Whitney *U*-test and analysis of variance for repeated measures were used in the statistical analysis, as appropriate. P-value less than 0.05 was regarded as statistically significant.
The ethical committee of the hospital had approved the study.

3. Results

During the study period, hypoglycemia was diagnosed in 465 neonates. Of these, 108 did not fulfill the inclusion criteria; 357 were eligible. The parents refused consent in 12 of these cases and in 224 cases the attending physician had no possibility to request consent because of lack of time, or lack of possibility to contact the mother. Sixty infants were allocated to the group 20% and 61 to the group 15%. (Figure 1)

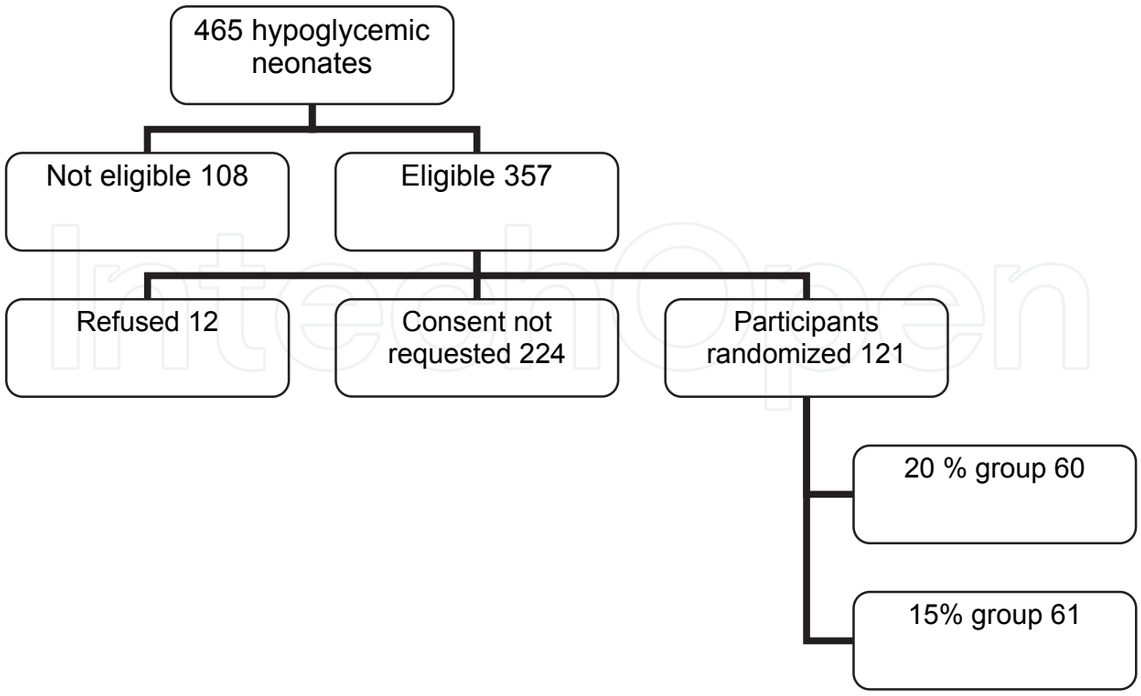

Fig. 1. Allocation of the study groups

The infants in the 20% and 15% groups were born at similar (mean (SD)) weeks' gestation (group 20% 39 (1.5) weeks vs. group 15% 39 (1.3) weeks) and birth weights (3605 (593) g vs. 3486 (626) g, respectively). Female/male ratios did not differ (23/38 vs. 24/36).
Similar percentages of infants in both groups had been delivered via caesarean section, were SGA or had birth weights >4500 g (Table 2). Few cases in either group were born from twin pregnancies and asphyxia was rare. Prematurity, need for phototherapy and antibiotic

	20% Glucose group	**15% Glucose group**
	N (%)	**N (%)**
Cesarean section	7 (12)	6 (11)
Small for gestational age (SGA)	0 (0)	2 (5)
Birth weight > 4500 g	2 (3)	3 (5)
Female/male	24/36	23/38
Twins	3 (5)	2 (3)
Premature	8 (13)	4 (7)
Five minute Apgar score < 7	2 (3)	4 (7)
Phototherapy	20 (33)	14 (23)
Intravenous antibiotics	12 (20)	6 (11)

The differences between the groups were not statistically significant

Table 2. Clinical characteristics of the infants in the study groups

treatment due to suspected or confirmed infection was more common in the group 20%, but the differences did not reach statistical significance. About half of the cases in both groups were infants of diabetic mothers (mean 30 (SD 49) % vs. 30 (SD 50) %). In the group 20%, 25 mothers and in the group 15%, 21 mothers had gestational diabetes, five versus nine mothers had type 1diabetes and seven versus 12 mothers were on insulin medication in the 20 and 15% groups, respectively, NS. Three mothers had pre-eclampsia in the group 20% and five in the group 15%. Ten mothers had hypertension in the group 20% and six in the group 15%. Ten mothers had signs of chorioamnionitis at delivery in the group 20% and six in the group 15%, respectively.

The concentrations of electrolytes in the glucose solutions, adjusted according to the plasma sodium and potassium levels, were similar in the two groups: the mean (SD) sodium concentrations being 38 (15) mmol/L versus 39 (12) mmol/L and potassium concentrations 12 mmol/L versus 13 mmol/L, respectively. Seven (12%) infants in the group 20% and 11 (18%) in the group 15% also received antibiotic treatment, the mean durations of antibiotic treatment being 6.0 (0.6) versus 5.2 (1.3) days, NS.

The mean (SD) duration of cannulation was in the group 20% 4.2 (1.4) days and in the group 15% 3.9 (1.3) days, NS. The number of cannulation site changes were median 1 (range 0–5) in the group 20% and 1 (range 0–6) in the group 15%, respectively, NS. In the 20% group 35 infants (59%) and in the 15% group 36 (60%) had some signs of phlebitis, NS. The cumulative severity score for phlebitis was low in both groups, in the 20% glucose group a median of 1 (range 0–7) and in the 15% group 1 (range 0–8), NS.

When the infants, who received antibiotics, were omitted, in infants receiving only intravenous glucose infusions, the mean (SD) duration of cannulation was in the group 20% 4.0 (1.3) days and in the group 15% 4.0 (1.3) days, NS. The number of cannulation site changes were median 1 (range 0–6), and 1 (range 0–5), respectively, NS. In the 20% group 31 (63%) and in the 15% group 33 infants (61%) had some signs of phlebitis, NS. The cumulative severity score for phlebitis was in the 20% group median 1 (range 0–8) and in the 15% glucose group 1.5 (range 0–8), NS.

Average plasma glucose levels were similar in both groups in the 20% group 4.6 (0.41) and in the 15% group 4.5 (0.37) mmol/L. High plasma glucose levels occurred in nine cases in the 20% glucose group and in 11 in the 15% group, and low levels in 37 versus 43 infants in the 20% and 15% groups, respectively, NS.

Weight as a function of infusion time and relative weight changes in the two groups were similar (Figure 2), NS.

4. Discussion

A recruitment bias is possible in this cohort in that the attending physician was not able to contact some mothers to obtain informed consent. A significant number of eligible infants were thus left out. This circumstance can be explained by the fact that a substantial proportion of hypoglycemia cases are admitted outside office hours, during which time the paediatricians on call are often too busy, and during the night reluctant to disturb the parents' sleep in order to recruit their baby for the study. It is also not possible to postpone the start of intravenous glucose infusion for long in hypoglycemic patients.

Maternal diabetes mellitus is one of the most important risk factors for neonatal hypoglycemia, and its severity might affect the need and duration of intravenous glucose infusion of the infants. Both small and large birth weight for gestational age might also be

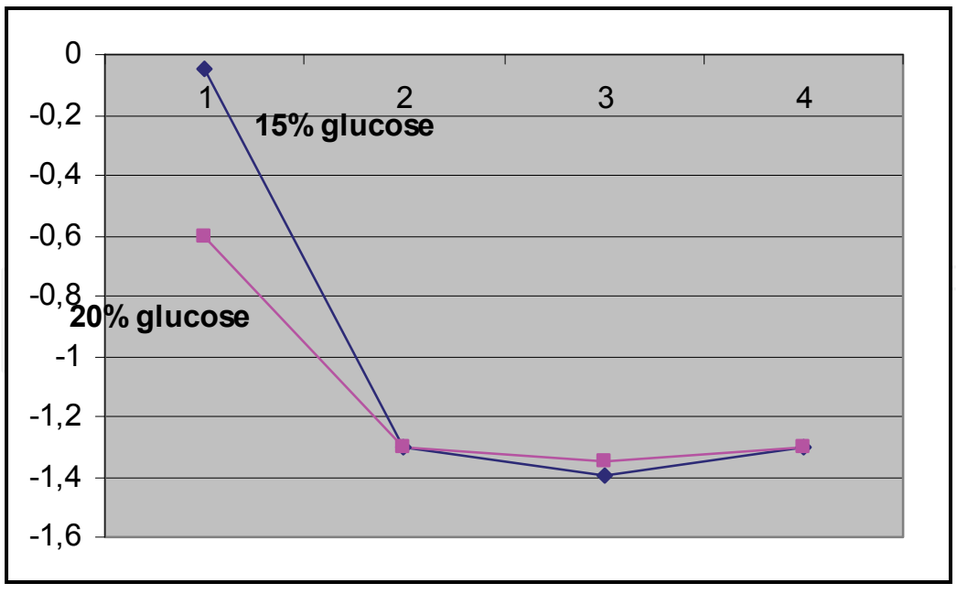

Fig. 2. Relative change in weight (% from birth weight) during intravenous glucose infusion. Circles indicate the 15% glucose and squares the 20% glucose group. X axis: weight changes. Y axis: time (days).

associated with a prolonged need of intravenous glucose infusion. The groups were, however, quite well matched for the percentages of mothers having gestational diabetes, type 1diabetes, for receiving insulin medication, and percentages of either SGA or LGA infants. Breast milk feeding is a cornerstone in the prevention and management of neonatal hypoglycemia, and weaning from intravenous glucose infusion is not possible without a successful feeding. The same feeding protocol was used in both groups.

Concomitant use of intravenous antibiotics during intravenous glucose infusion increases obviously the risk of phlebitis, and is therefore a confounding factor in the comparison between 15% and 20% glucose groups. The percentage of infants receiving antibiotics was somewhat, although not significantly higher in the 20% group. The higher osmolarity of the 20% glucose solution was, however, not associated with an increased rate or severity of phlebitis in our infants. In addition, omitting the antibiotic-treated cases did not change the result. The electrolyte concentrations in the 15 % and 20 % glucose infusion fluids were similar. As intravenous glucose was administered at the same rate (mg/kg/min) in both study groups, the 15% glucose group received fluids at a 33% higher rate than the 20% glucose group. The differences in fluid infusion rates might even have balanced the local effect of different glucose concentrations on the vessel wall at the infusion site.

The clinical classification of phlebitis also involves risk of bias, as observation and classification is subjective. The observers rating the severity of the phlebitis were not aware of the glucose concentration used in each case. Accidental detachment of intravenous lines occurs only rarely and the most common reason for a cannulation site change is local irritation and swelling at the infusion site. The number of cannulation site changes would thus seem to be a fairly objective measure of extravasation of fluids. According to earlier work, extravasation of peripheral fluid infusions occurs by 36 h in more than half of the patients (Möller, et al., 1996, Hecker et al.,1991). In our patients the mean duration of cannulation was about four days in both groups, suggesting that the median number of

cannulation changes in the cases on both groups is in accordance with the previous data. Thus, the duration of cannulation, number of cannulation changes and phlebitis severity scores were similar in both groups. One can assume, that the safety of peripheral 20 or 15% glucose intravenous infusions is similar also in neonates, who need intravenous glucose infusions for other reasons than hypoglycemia, including short-term parenteral nutrition.

The occurrence of phlebitis has been evaluated in adults in a comparison of peripheral infusions of nutrient solutions with and without 20% fat emulsion (Daly JM et al., 1985). Adding fat to the fluids did not protect the veins from the development of phlebitis. Infiltration was more dependent on the catheters than on the osmolarity of solutions. In keeping with this, peripheral intravenous nutrition caused phlebitis in all patients using Teflon cannulas, but in only 7% using silicone catheters. The risk of phlebitis was very low even when nutrition solutions of an osmolarity of 1250 mOsm/kg were administered via the latter catheters (Madan M et al., 1992). In our study, the same peripheral catheters were used in both groups and therefore the role of catheter type in the development of phlebitis cannot be established here.

Although infants in the 20% glucose group received 33% less fluids than those in the 15% group, no differences in weight changes were seen. Our infants were all quite healthy, having no or mild neonatal problems in addition to hypoglycemia and would thus seem to tolerate excess amounts of fluids well. Our study was not powered to establish, whether less fluid intake would be beneficial by decreasing risk of respiratory problems and need of oxygen supplementation in the 20% glucose group compared to the 15% glucose group. In patients who do not tolerate fluids normally, as in cases of birth asphyxia, renal failure, bronchopulmonary dysplasia or inappropriate antidiuretic hormone excretion, reduction of fluid intake by using 20% instead of 15% glucose might have beneficial effect on the outcome of the patient.

5. Conclusion

Intravenous 20% glucose solutions can be infused into peripheral veins as safely as 15% glucose solutions. The risks of excess fluid intake, in addition to oral feeding, need to be established in further studies in infants with neonatal hypoglycemia.

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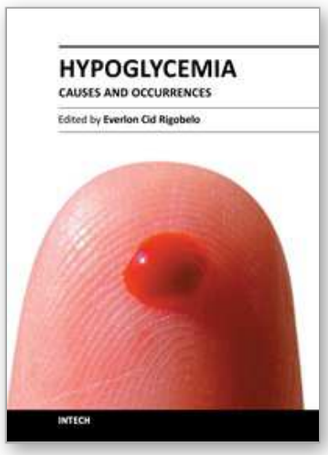

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Glucose is an essential metabolic substrate of all mammalian cells being the major carbohydrate presented to the cell for energy production and also many other anabolic requirements. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the glucose serum concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. This book provides an abundance of information for all who need them in order to help many people worldwide.

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