HYPOGLYCEMIA IN SICK PRETERM INFANTS AND THE THERAPEUTIC EFFECT OF 12.5% DEXTROSE IN WATER COMPARED WITH 10% DEXTROSE IN WATER

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Abstract- Neonatal hypoglycemia is common and its prompt management is important to reduce neurological sequelae. To determine the effect of two different glucose concentrations of intravenous (IV) fluid therapy in the incidence of hypoglycemia in sick premature infants, 200 preterm infants weighing 1500-2500 g were selected and randomly assigned into two groups. Group 1 received 10% dextrose in water (DW) and for group 2 we used 12.5% DW with recommended fluid volume according to the infant's condition. First blood glucose sample was obtained during 2-3 hours of life before starting IV therapy and the two others were measured between 4-24 hours of life after starting IV fluid therapy. Plasma glucose < 36 mg/dl during 2-3 hours of life and level below 45 mg/dl between 4-24 hours of life were considered as hypoglycemia. Birth weight, gestational age and type of diseases in two groups were matched. Although there was no difference between volume of fluid, statistical differences were found to be significant between amounts of calories (P = 0.000) and dextrose (P = 0.000) received in two groups. We detected 15 and 30 cases of hypoglycemia in group 1 and 2, respectively. After starting IV fluid therapy, the incidence of hypoglycemia decreased especially in group 2 and comparison of cases with two consecutive low plasma glucose in two groups showed significant difference (P= 0.024, relative risk= 2.67). We recommend 12.5% DW when initiation of peripheral IV therapy is indicated in sick preterm infants weighing 1500-2500 g, especially when restriction of fluid is mandated.

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Key words: Hypoglycemia, intravenous fluid therapy, preterm infant

INTRODUCTION

Parenteral fluids are commonly used to treat or prevent hypoglycemia, but the underlying principle of fluid and electrolyte management of the sick preterm infants is to prevent, or at least decrease the likelihood of significant pulmonary and extra pulmonary edema formation. Accumulating clinical evidence demonstrates that positive fluid balance adversely affects the course and complications of respiratory distress syndrome. An association between high fluid intake and an increase incidence of patent ductus arteriosus, congestive heart failure, necrotizing enterocolitis and bronchopulmonary dysplasia has been demonstrated (1).

Measures to prevent these problems include provision of negative fluid and electrolyte balance during the first week of life by restricting fluid and salt administration (2). However, fluid restriction entails the risks of hypoglycemia, hyperosmolality and hypoperfusion with metabolic acidosis (1).

Generally, 10% dextrose in water (DW) is recommended with ranges of 65-96 ml/kg for the first 24 hr of life. Infused through a peripheral vein, this

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range can produce 4.5 to 6.6 mg/kg/min glucose in these patients (1, 3, 4). While the glucose production rate in term newborns is approximately 3 to 5 mg/kg/ minute, premature infants have somewhat higher rates of basal glucose production, and utilize up to 7.7 to 7.9 mg/kg/min (5). Without considering glucose requirements, constriction of fluids could produce some discrepancies between volume and glucose needs in these infants. To provide basic guidelines by which define hypoglycemia, Cornblath and others issued a consensus statement about operational thresholds for blood glucose concentrations. They proposed to keep plasma glucose levels above 2.5 mmol/L in high risk infants with underlying disease at all times (6). Yager suggested that blood glucose concentrations < 2.7 mmol/L must be viewed with concern and as a threshold for monitoring and intervention (7).

Considering Cornblath *et al.* criteria for definition of hypoglycemia and Yager recommendation, we compared the effect of 10% DW as proposed in literature with the same volume from 12.5% DW, which is the highest concentration of glucose that can be infused through a peripheral line (8), and measured the incidence of hypoglycemia during the first 24 hours of life.

MATERIALS AND METHODS

From January to July 2003, 200 sick preterm infants with birth weight of 1500 to 2500 g were randomly assigned into two groups at the maternity hospital, Tehran University of Medical Sciences. We obtained informed consent from all parents.

Clinical symptoms of patients did not permit to start oral feedings from the first hour of life. In group 1, fluid therapy was started with 10% DW, and group 2 received 12.5% DW. First sample of plasma glucose (PG) concentration was measured before starting intravenous (IV) fluid therapy during 2-3 hours of life. Subsequently two other samples were obtained during 4 to 24 hours of life and immediately transported to lab. All the measures were performed before any change in IV glucose concentration or volume of fluid. The method for glucose determination in the laboratory was automatic analysis technique with glucose oxidase. For further evaluation, other blood glucose concentrations were assessed by test strip, which was not included in the study. PG < 36 mg/dl (2.0 mmol/L) during 2-3 hours and < 45 mg/dl (2.5 mmol/L) for the rest of 24 hours were recognized as hypoglycemia.

Demographic data like gestational age, birth weight, growth curve, type of diseases, volume of fluid therapy and amounts of calories and glucose used were compared in two groups by *t* test, Chi square and Fisher exact tests.

RESULTS

One hundred sick preterm neonates with 3 samples of PG concentrations entered each group. The differences between birth weights, gestational ages, and predisposing factors for hypoglycemia were not significant in two groups (Table 1).

Although there was not a significant difference between volumes of fluid therapy in two groups, significant difference was demonstrated between amount of glucose and calories received (Table 2).

Comparison of mean of blood glucose levels showed significant difference between two groups except in the first sample, which was before starting IV fluid therapy (Table 3).

Table 1. Comparison of birth weight, gestational age and predisposing factors of hypoglycemia in studied groups*

Variable	Group 1	Group 2	*P*
Birth weight	1929.1±325.5†	1904.5±290.2†	0.573
Gestational age	33.6±2.0†	33.40±1.9†	0.321
Predisposing factors			
Asphyxia	6	12	0.43
Diabetic mother	5	6	0.7
IUGR	8	10	0.8
RDS	41	44	0.77
Polycythemia	1	2	1.0
Clinical sepsis	55	49	0.57
Pneumonia	12	10	0.65

Abbreviations: IUGR, intrauterine growth retardation; RDS, respiratory distress syndrome.
*Data are given as number unless specified otherwise.
† mean ± SD.

Table 2. Volume of fluid and amount of calorie and sugar received in studied groups*

Variable	Group 1	Group 2	*P*
Fluid (cc/kg/d)	71.4±12.5	72.3±8.1	0.561
Calories (kcal/kg/day)	28.9±3.7	36.0±5.1	0.000
Sugar (mg/kg/min)	5.034±0.6	6.245±0.7	0.000

* Data are given as mean ± SD.

We found 15 cases of hypoglycemia in group 1 and 30 in group 2 with a total incidence of 22.5%. After starting IV fluid therapy, the incidence of hypoglycemia was 35% and 18% at the time of second sampling and 27% and 12% at the third sampling in groups 1 and 2, respectively. Comparison of incidence of hypoglycemia showed significant statistical difference (P= 0.006, RR= 1.94 and *P* = 0.007, RR = 2.25), and few cases of hyperglycemia (PG level > 150 mg/dl) were detected in both groups (Table 4).

If two consecutive low PG (< 45 mg/dl) concentration in the second and third sampling were considered, there were 16 and 5 cases in group 1 and 2, respectively. The statistical difference was significant (*P* = 0.024, RR= 2.67) (Table 5).

Two consecutive PG concentrations > 150 mg/dl in second and third samplings were considered as hyperglycemia which were found in one and three cases in groups 1 and 2, respectively.

DISCUSSION

Hypoglycemia remains a common and controversial problem of newborn infants. Despite the issues surrounding the problem, a review of the literature allows for the appropriate recognition of the infants at risk and institution of a plan for monitoring and therapeutic intervention.

Table 3. Mean of glucose levels in studied groups*

Variables	Group 1	Group 2	*P*
Average PG	64.8±26.1	81.2±42.6	0.001
1st PG†	61.5±37.1	59.5±45.9	0.742
2nd PG†	67.0±44.5	92.2±76.3	0.005
3rd PG†	66.0±30.2	91.9±61.7	0.000

Abbreviation: PG, plasma glucose.
*Data are given as mean± SD.
† Time of sampling.

Table 4. Incidence of hypo/hyperglycemia in first, second and third samplings*

Variables	Group 1	Group 2	*P*	RR
Hypoglycemia				
1st†	15	30	0.011	1.4
2nd†	35	18	0.006	1.9
3rd†	27	12	0.007	2.2
Hyperglycemia				
1st†	3	5	0.36	1.08
2nd†	5	10	0.179	0.5
3rd†	1	5	0.22	0.10

Abbreviation: RR, relative risk.
* Data are given as number.
† Time of sampling.

Unfortunately, in developing countries, growth retardation, hypothermia, practice of late feeding and maternal malnutrition are additional risk factors that worsen the situation and it may not be appropriate to apply the guidelines described in developed countries to these countries (9). The most significant factor in the decision to treat is the definition of true hypoglycemia. Regarding ambiguity surrounding a precise definition, Koh *et al.* surveyed 36 pediatric textbooks and 176 pediatric consultants to search for an agreement on the definition of neonatal hypoglycemia. Perhaps not surprisingly, there was none; definitions ranged from less than 1 mmol/L to less than 4 mmol/L (10). According to Yager *et al.*, institution of therapy should be considered in any infant who displays low blood glucose concentrations, particularly on more than one occasion, has symptoms of hypoglycemia or borderline glucose concentrations with concomitant underlying pathology (7).

We considered hypoglycemia based on Cornblath *et al.* and Yager suggestions (6, 7). All of our patients were sick and showed symptoms such as hypotonia, respiratory distress, hyporeflexia, irritability, jitteriness and other non-specific symptoms. We could not differentiate the hypoglycemic symptoms

Table 5. Number of patients with two consecutive low plasma glucose in 2nd and 3rd samplings*†

Group	Hypoglycemic	Not hypoglycemic
1	16	84
2	5	95
Total	21	179

*Data are given as number.
†Statistical difference was significant with *P* of 0.024 and relative risk of 2.67.

from the symptoms of underlying diseases.

It should be appreciated that symptoms of hypoglycemia are often vague and nonspecific (11) and although attempts have been made to define hypoglycemia by correlating blood glucose concentration with clinical signs and symptoms, this approach has not been successful (12). The so-called asymptomatic hypoglycemia is also found in neonates at risk of hypoglycemia and abnormal evoked potentials has been recorded in these neonates despite PG < 2.6 mmol/L. Glucose levels below this limit may cause disturbance of CNS function due to low energy accessibility (11).

It is difficult to comment on the prevalence of hypoglycemia in the groups at risk. There are also few published data regarding the prevalence of hypoglycemia in developing countries (9). In our study, incidence of hypoglycemia before starting IV fluid therapy was 22.5%. After starting glucose, although two groups were similar with respect to volume of fluid and type of disorders, increasing amount of glucose in IV fluid in second group decreased the incidence of hypoglycemia with significant statistical difference. For further reliability, we compared two consecutive low PG concentrations after IV fluid therapy, and the results also showed significant statistical difference. Short term hypoglycemia is generally believed to be harmless but it is possible that previous energy restriction as in neonates with intrauterine growth retardation or congenital infections in combination with shorter periods of hypoglycemia cause permanent CNS damage (11).

No study on human neonates has addressed the duration of hypoglycemia which is harmful, but a study on neonatal monkeys demonstrated that 10 hours of severe hypoglycemia is associated with motivational and adaptability problems 8 months later (13). It is suspected that prolonged periods (at least 12-24 hours in the at risk groups of human neonates) may lead to neurological sequelae (7, 9). It is possible that severe prolonged hypoglycemia may have long term as well as acute neurological effects, especially if there are coexisting adverse perinatal events such as asphyxia (14, 15).

In developing countries, where lack of resources interfere with following the standard protocols for screening high-risk neonates for hypoglycemia, this common problem could be prolonged; prudent practice could minimize the complications. In this study not all hypoglycemic cases at the time of second sampling were hypoglycemic at the time of third sampling. If we accept that the level of PG concentration in the body is the result of consumption and production of glucose according to liver's ability and other mechanisms like counter regulatory hormones (6), then it is not far to see these fluctuations and if we could prevent it, then the resulted complications might be decreased. With respect to reducing episode of hypoglycemia at the time of third sampling in group 2, increasing IV glucose concentrations might be useful to catch this goal.

Neonatal hypoglycemia is a common but usually preventable condition. Its prompt recognition, prevention and management are important to reduce the unquantified but worrying risk of neurological sequelae. Using some kind of measures like increasing IV fluid concentration of dextrose especially in conditions when restriction of fluid volume is mandated, could shorten the duration and incidence of hypoglycemia.

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