Controversies in the Management of Hyperglycemia in the ELBW Infant

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ABSTRACT

Hyperglycemia is a common problem in newborns undergoing intensive care, especially extremely low birth weight (ELBW) infants. There is a lack of consensus with regard to various aspects of management of neonatal hyperglycemia including definition, optimal management strategy as well as short and long term implications. We reviewed the current evidence in this regard. Recent studies suggest that adequate control of hyperglycemia may be beneficial but long-term implications of hyperglycemia and insulin therapy in the ELBW infants are not known. Awaiting further research, it may be pragmatic to use a more operational definition of hyperglycemia and limit insulin therapy to neonates with high risk of osmolar derangement as per the proposed guideline.

Key words: *Extremely low birth weight infants, Glucosuria, Hyperglycemia, Insulin.*

INTRODUCTION

Hyperglycemia occurs in 60 to 80% of extremely low birth weight infants (ELBW) and may impact upon their morbidity and mortality(1,2). Historically, neonatal hyperglycemia has been linked to adverse neurological outcome but there is no concrete evidence to support this. Moreover, there is lack of consensus with regards to diagnosis and management of neonatal hyperglycemia. We therefore explored current literature regarding the definition, etiology, implications and management of neonatal hyperglycemia.

DEFINITION OF HYPERGLYCEMIA

There is no established definition of neonatal hyperglycemia and the upper safe limit of blood glucose in this population has not been determined(3-5). Various researchers have suggested whole blood glucose >125 mg/dL (6.9 mmol/L) or plasma glucose >150 mg/dL (8.3 mmol/L) as a reasonable cut-off, this being the renal glucose threshold of well premature infants(6,7). Moreover, the effects of neonatal hyperglycemia may be influenced by duration, peak levels, gestation and clinical stability(8,9). It is pertinent to note that neonatal hyperglycemia may be a sign of serious illness such as infection and management of the underlying illness is much more important than just achieving a target glucose level. Possible complications of neonatal hyperglycemia like dehydration, dyselectrolytemia and cerebral damage have been linked to osmolar changes(3). However, there is evidence to suggest that blood glucose level of >360 mg/dL (20 mmol/L) is required to produce significant osmolar changes(3). This level is much higher than currently used to dictate clinical practice. It may be pragmatic to monitor osmotic diuresis instead of targeting a safe blood glucose level in isolation(9). In a recent review by Hey(5), blood glucose ≥216 mg/dL (12 mmol/L) was suggested as a useful operational definition of hyperglycemia(5). This however, should not constitute the cut-off level to treat hyperglycemia but instead should serve as a cut-off to investigate and monitor and look for evidence of osmotic diuresis.

In clinical practice, the presence of ≥1% of glucosuria (≥1000 mg/dL or 56 mmol/L of urinary glucose) may suggest a risk of osmolar changes and thus warrants strict glucose monitoring(9). Sequential analysis of urine spot samples for glucose and osmolality has been suggested as a feasible way of monitoring the infants at risk and may serve to decrease iatrogenic blood loss(5).

MEASUREMENT OF BLOOD GLUCOSE

Blood glucose can be estimated from whole blood, plasma or serum using laboratory performed hexokinase and glucose-oxidase method and point-of-care reflectance glucometers. In general, whole blood glucose measurements are 10-15% lower than plasma glucose concentrations depending on the hematocrit and the method of whole blood analysis. Point-of-care blood gas and metabolite analysers provide a fast and reliable means of measuring blood glucose using small volumes of blood(10). Although point-of-care glucose meters (Accu-Chek, Accutrend, Elite, HemoCue, Omni) are increasingly used for making therapeutic decisions they are known to show marked variability with central laboratory analyzer especially at the hypoglycemic and hyperglycemic ends of the spectrum(11). The glucose-oxidase method using Yellow Springs Instrument (YSI; YSI Inc, Yellow Springs, Ohio, USA) is frequently used and generally accepted as a reference analyser(11). Other methods of blood glucose measurements are also available but lack experience in neonatal population. Blood glucose measured by the minimally invasive transdermal approaches rely either on the interaction of electromagnetic radiation with the tissue or on the extraction of fluid across the barrier by application of physical energy. A device using reverse iontophoresis [the GlucoWatch Biographer (Cygnus, Inc., Redwood City, CA)] is already commercially available whereas sonophoresis and microporation method, for example, are in relatively early-stage development. The truly non-invasive optical techniques (near-infrared and Raman spectroscopy, polarimetry, light scattering, and photoacoustic spectroscopy) monitor blood glucose by analysis of the absorbed or scattered radiation, to provide a measure proportional to the concentration of glucose in the dermal tissue. By contrast, impedance spectroscopy measures changes in the dielectric properties of the tissue induced by blood glucose variation. Glucose analysis of the body fluids such as saliva, sweat, urine and tears are also available although they correlate poorly with well established blood glucose analysers. Large-scale studies in support of efficacy of these methodologies are awaited and an affordable, efficient, and portable system is not on the immediate horizon(12).

INCIDENCE

Hyperglycemia is estimated to occur in 60 to 80% of ELBW infants(13,14). The variation in incidence is most likely due to the disparity in the definition of hyperglycemia as well as in the study populations. The incidence of neonatal hyperglycemia seems to be rising with the improved survival of ELBW infants and perhaps due to early and aggressive use of parenteral nutrition(3).

GLUCOSE HOMEOSTASIS AND ETIOLOGY OF HYPERGLYCEMIA

Glucose is the primary energy substrate in the early neonatal period and is the main source of energy to the central nervous system(15). Since glycogen storage does not occur till the third trimester, the ELBW infant has a limited reserve(15). This deficiency is compounded by the relatively higher energy requirements of the ELBW infant. At birth, following cessation of the maternal glucose supply, the newborn maintains glucose homeostasis by a complex interplay of glucoregulatory hormones affecting hepatic glycogenolysis and gluconeogenesis(16,17). Perturbations of glucose homeostasis are common in this transitional phase. In preterm, growth restricted and sick infants with low metabolic reserves and a limited hormonal response, these transient disturbances may be more pronounced(17,18). Even though hypoglycemia is the most common derangement in glucose homeostasis in the newborn period, hyperglycemia is not uncommon, especially in preterm and growth restricted infants(3,16,17).

Insulin, an important player in glucose homeostasis, facilitates glucose uptake by activating a specific glucose transporter on skeletal and cardiac

muscle, adipose tissue and alpha cells of pancreas. Immediate effects occurring within seconds include increased transport of glucose, amino acid and potassium into insulin sensitive cells(19). The main actions that occur over minutes include stimulation of protein synthesis, suppression of protein degradation and activation of enzymatic pathways involved in the synthesis of glucose. Delayed effects may take hours and include stimulation of mRNA synthesis for lipogenic activities.

Neonatal hyperglycemia may be related to a high glucose production, low uptake or high exogenous glucose infusion(3). The inability of preterm infants to inhibit gluconeogenesis in response to intravenous glucose has been well documented(20). It has been suggested that defective processing of proinsulin and relative insulin resistance may be largely responsible for hyperglycemia(16,21). Neonates, especially the sick preterm infant may also demonstrate a lower or delayed secretion of insulin in response to a glucose load(3). They also have a lower peripheral sensitivity to insulin and decrease response to a particular concentration of insulin(19). Insulin resistance may be related to immaturity or down regulation of peripheral receptors(3). Counter-regulatory hormones may also contribute to hyperglycemia(3). Moreover, early and aggressive use of parenteral nutrition may contribute to high glucose intake. Administration of intravenous fat emulsion has been shown to increase plasma glucose concentration by 24% over baseline values. Additive effect has been noted when glucose and amino acids were added to the intravenous fat emulsion(22). Thus lipids contribute to hyperglycemia which causes paradoxical increase in insulin due to increase in the free fatty acids that gets oxidised in preference to glucose. Additionally, lipids suppress the hepatic effects of insulin and decrease its peripheral action. In contrast amino acids such as leucine, valine, isoleucine, glutamine and arginine known as insulin secretogouges offer protection as they are required for the normal growth of pancreas and the beta cells. Considering the relatively higher glucose infusion rate, low glucose uptake rate, and defective glucoregulatory hormone control, hyperglycemia is no surprise in the neonatal intensive care (NICU) population. Clinical stresses such as infection, respiratory distress, hypoxia, pain and surgical procedures may also contribute to hyperglycemia(3).

The transport of the polar glucose molecule through biological membranes is catalysed by facilitated glucose transporters, the GLUT or SLC2 gene family(23), and the sodium-coupled glucose cotransporters, the SGLT or SLC5 gene family(24). ***Table* I** details the predominant glucose transporters. Ongoing research in this field may bring forth novel therapies for management of hyperglycemia and diabetes.

In contrast to the commonly encountered transient hyperglycemia, neonatal diabetes mellitus is considered to be a very rare entity. Both permanent and transient neonatal diabetes mellitus (TNDM) have been delineated with evidence of abnormalities in chromosome 6 in a significant proportion of TNDM(25,26). It is not clear whether the typically observed hyperglycemia in the neonatal population and TNDM are extreme ends of the same spectrum or totally different entities.

IMPLICATIONS OF HYPERGLYCEMIA

Historically neonatal hyperglycemia has been linked to osmotic diuresis and dehydration, dyselectrolytemia and intraventricular hemorrhage(7,8,27). However, evidence from well-designed studies is lacking. Blood glucose ≤230 mg/dL (13 mmol/L) may not result in osmotic diuresis(8,9) and concerns regarding cerebral damage due to fluid shifts in hyperglycemia have not been authenticated in the literature. However, it is pertinent to note that hyperglycemia in animal models is known to aggravate ischemic brain injury, possibly due to the activation of signalling pathways involving reactive oxygen species, Src and mitogen-activated protein kinases(28).

Recent studies in adults, children and neonates have demonstrated an association between hyperglycemia and increased mortality and morbidity (1,2,29,30). In adult surgical hyperglycemic patients, van Den Berghe, *et al.*(29). noted lower in-hospital mortality, bloodstream infections and number of red cell transfusions in the insulin treated group. Faustino, *et al's* recent study in the pediatric intensive care setting also suggests a correlation

TABLE I DISTRIBUTION AND FUNCTION OF MAJOR GLUCOSE TRANSPORTERS

Name	Major sites of expression	Main Function
GLUT 1	Erythrocytes and endothelial cells of blood-tissue barrier	Responsible for the low-level of basal glucose uptake required to sustain respiration in all cells.
GLUT 2	Liver cells, pancreatic β cells, renal tubular cells and small intestinal epithelial cells	Responsible for release of glucose into the circulation
GLUT 3	Neurons and placenta	Main glucose transporter isoform in the neurons
GLUT 4	Muscle, heart and adipose tissues	Responsible for insulin regulated glucose disposal
SGLT 1	Small intestinal mucosa and proximal tubule of nephron	Responsible for 2% of glucose reabsorption
SGLT 2	Proximal tubule of the nephron	Responsible for 98% of glucose reabsorption

between hyperglycemia and in-hospital mortality rate and length of stay(30). In ELBW infants, hyperglycemia has been associated with severe retinopathy of prematurity(31). The exact pathophysiology of such complications attributed to hyperglycemia needs to be elucidated. It has been postulated that increased free oxygen radical formation is causally related to diabetes-related congenital malformations and are mediated by sorbital accumulation, arachidonic acid and myoinositol deficiencies and high concentrations of beta-hydroxybutyrate(32). The aforementioned recent studies have rekindled interest in hyperglycemia and brought forth questions with regard to appropriate diagnosis and management.

Replication of normal *in-utero* fetal growth is considered a standard for postnatal nutrition in preterm infants(33). This is difficult to achieve due to the low energy stores of the preterm infant coupled with a high metabolic rate. Early nutrition has been shown to affect neurodevelopmental outcome(34) and may also play a role in the incidence of chronic lung disease and late onset sepsis in the NICU. Lowering the intake of parenteral glucose is still widely practised for treatment of neonatal hyperglycemia(13,35,36). In addition to the direct effects of hyperglycemia, restriction of calorie intake may in itself have significant implications. In contrast Zylberberg, *et al.*(37) have proposed the use of insulin over a prolonged period to enhance weight gain in very low birth weight infants (VLBW). They reported a shortening of hospital stay and weight gain closely matching intrauterine growth in the insulin treated neonates. However, in the absence of studies investigating the long-term implications of insulin therapy such an approach is not advisable.

CURRENT MANAGEMENT

The standard approach to the management of hyperglycemia in the neonate involves the use of glucose restriction or exogenous insulin therapy to achieve euglycemia and improve nutritional uptake(15,38). A combination of glucose restriction and insulin therapy is also practiced. There is significant variation between individual units and amongst neonatologists. The resting energy expenditure in premature infants is considered to be about 60 kcal/kg/day with total body basal consumption of glucose about 0.2 mmol/kg/minute (3.7 mg/kg/min)(17). The stable ELBW infant has been estimated to require a glucose supply rate of about 6 mg/kg/min with an additional 2-3 mg/kg/min to support protein anabolism(15). However, the demands of sick infants in the NICU may be much higher. Glucose restriction in this setting may cause caloric deprivation and suboptimal postnatal growth at a crucial period(39). There is mounting evidence that early nutrition has a significant impact on both short and long term morbidity(34,40) and thus glucose restriction may not be desirable.

The maximal glucose oxidative capacity in the neonate appears to be about 12 mg/kg/min(15) and beyond this level conversion to fat occurs. Since the conversion of glucose to fat is not energy efficient this may lead to a higher oxygen consumption and

increased production of carbon dioxide. It thus seems appropriate that glucose infusion rate for preterm neonate be targeted between 6-12 mg/kg/min, depending upon the gestation and clinical stability.

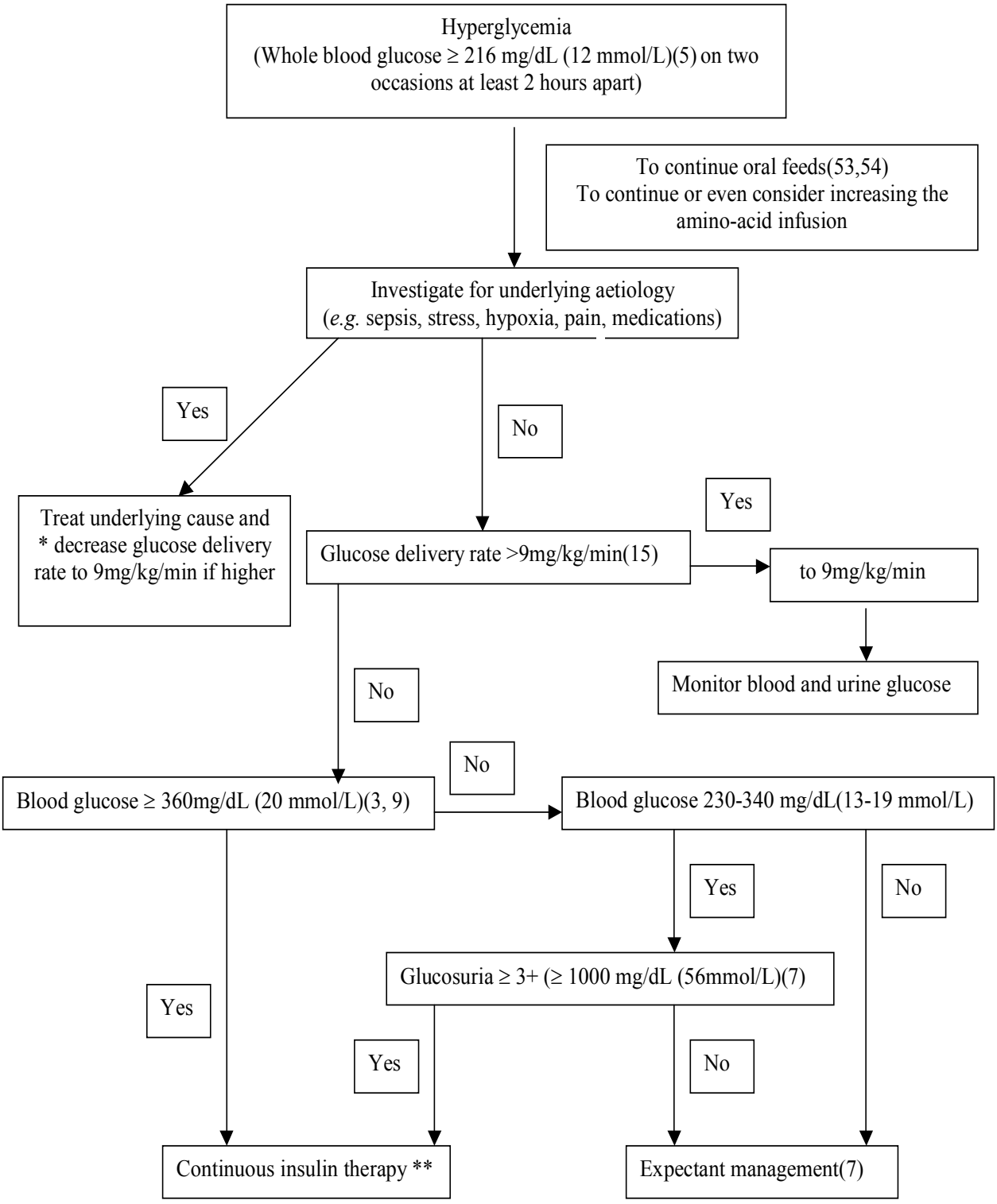
Insulin infusion has been used to promote substrate tolerance without having to restrict calories(14,19,35-38,41-46) but may cause hypoglycemia and hypokalemia. Moreover, the use of insulin to enhance nutritional uptake may lead to development of significant lactic acidosis(15). Further, the long-term clinical significance of large doses of exogenous insulin in association with early high-energy intakes in the preterm neonate is unknown.

PRESENT EVIDENCE

The lack of consensus regarding optimal management of neonatal hyperglycemia is a reflection of the inadequacy of current evidence regarding best practice. There have been only 2 randomized trials(35,36) evaluating efficacy of insulin therapy *vis-a vis* glucose reduction but both had small sample sizes. There are 7 case series(14, 41,42-46) reported in the literature regarding the use of insulin for neonatal hyperglycemia, involving over 250 neonates. Out of these only 1 study (14) included a control group.

Meetze, *et al.*(36) randomized ELBW infants on day 2 of life to receive insulin infusion or glucose reduction when hyperglycemic (single blood sugar >240 mg/dL (13.3 mmol/L) or repeat blood glucose >160 mg/dL (8.8 mmol/L) for at least 4 hours) following sequential increment in glucose intake. Infants whose blood sugars remained normal served as a control group (n = 33). The primary outcome measure of number of days required to achieve 60 kcal/kg/day of non-protein energy was significantly lower in the insulin group (P <0.01). Collins, *et al.* (35) in a prospective randomized controlled trial involving 24 ELBW with hyperglycemia reported a significantly better calorie intake (124.7 ± 18 versus 86 ± 6 kcal/kg/day) in the insulin group compared to controls who received glucose reduction for hyperglycemia (180 mg/dL (9.9 mmol/L) + glycosuria). Weight gain in the insulin group was also significantly better (20.1 ± 12.1 versus 7.8 ± 5.1 g/kg/day). Binder, *et al*.(14) in a retrospective case review involving 76 ELBW infants with hyperglycemia compared 34 infants who received insulin therapy with 42 who did not. Duration to regain birth weight and achieve nutritional intake of 100 kcal/kg/day was similar in the two groups. However, the discharge weight in the insulin group was significantly higher despite having a lower birthweight and gestational age. Heron, *et al*.(43) noted a significant improvement in calorie intake following insulin infusion (60.8 ± 25.1 to 79.9 ± 24.5 kcal/kg/day, P<0.001) in a case series involving 15 ELBW(43). Vaucher, *et al*.(41) in a case series of 10 VLBW infants with hyperglycemia demonstrated an increase in calorie intake from 29 to 56 kcal /kg/day with the use of insulin infusion. Ostertag, *et al*.(42) in their case series of 10 VLBW infants with hyperglycemia also noted an improvement in glucose tolerance following insulin infusion, with increase in mean calorie intake from 49.5 to 70.4 kcal/kg/day. They also noted significant improvement in weight gain whilst on insulin therapy. In 30 VLBW hyperglycemic infants receiving parenteral nutrition, Thabet, *et al.*(45) noted improvement in intravenous glucose tolerance (14 mg/kg/min) and higher calorie (non protein calorie 121 ± 16 kcal/kg/day) intake whilst on insulin infusion.

Meetze, *et al.*(36) achieved euglycemia in 14/14 in the insulin group compared to 9/11 in the glucose reduction group. Euglycemia (70 to 140 mg/dL (3.9 to 7.7 mmol/L) was achieved equally in both groups in the study by Collins, *et al*.(35). Although Meetze, *et al*.(36) reported no episodes of hypoglycemia in either group (blood glucose <60 mg/dL (3.3 mmol/L), Collins, *et al*.(35) documented hypoglycemia in 4 among 1848 measurements in the insulin group. In Binder, *et al*.(14) retrospective study, the incidence of hypoglycemia (<40 mg/dL (2.2 mmol/L) was 0.5% (26/7368 measurements). Vaucher, *et al.*(41) and Ostertag, *et al.*(42) also reported a low incidence of hypoglycemia (0% and <1% respectively) but the cut-off for hypoglycemia was much lower than standard practice (<25mg/dL (1.4 mmol/L). The incidence of hypoglycemia was highest in the series of Heron, *et al*. (2.8%)(43), who used blood glucose <36 mg/dL (2.0 mmol/L) as cut-off. In summary, hypoglycemia remains an important complication of insulin therapy and warrants close monitoring.



** The maximum reduction in glucose infusion in ELBW infants that can be done and is physiological is up to 6 mg/kg/min.*
*** Monitor and add potassium to intravenous fluids if serum potassium less than 3.5 mmol/L (ensure renal function is adequate).*

FIG. 1. *Guideline for the management of neonatal hyperglycemia.*

However, since the definition of hypoglycemia varied significantly between the various studies, the true incidence is difficult to ascertain.

Ng, *et al*.(46) divided 115 hyperglycemic neonates into two groups using a birth weight of 1000 g as cut-off and compared response to insulin therapy. They concluded that insulin therapy was effective in glycemic control in both groups, though insulin requirement was significantly higher in the ELBW. No serious adverse side effects were noted. Kanarek, *et al*.(44) noted improved glucose tolerance in two groups of VLBW on insulin therapy and parenteral nutrition, with and without addition of lipid emulsion.

Potential benefits of controlling hyperglycemia have been suggested in intensive care settings outside neonatology as well. In adult post surgical and burn injury patients, uncontrolled hyperglycemia has been associated with increased episodes of sepsis(47,48). Recent studies involving use of insulin for rigid blood glucose control in hyperglycaemic adult intensive care patients have shown significant decrease in their mortality, intensive care stay and incidence of sepsis(29,49). Studies in patients with post myocardial infarction have also suggested an improved long-term outcome in patients who received insulin and had better glycemic control(50). The contribution of anabolic effects of insulin to these beneficial effects is difficult to delineate.

The rationale of using insulin therapy in ELBW infants has a physiological basis. The early neonatal period is marked by insulin resistance and or relative insulin deficiency(3,21). Moreover, fetal growth restriction in animal models has been shown to be associated with impaired pancreatic development and a reduced β-cell mass(51), which may further compromise glucose homeostasis in this group of infants. Establishment of oral feeds and the coupling of food-related nutrient and hormonal signals increase the release of insulin(52). Minimal enteral feeds are also known to promote pancreatic function by inducing the gut production of enteroinsular hormones also known as incretins like GIP and pancreatic polypeptide(53,54). However, in the ELBW infants, it may not be possible to initiate oral feeding and thus induce normal insulin secretion. This leads to prolongation of the catabolic state and as a consequence birth weight may not be regained for several weeks. Insulin replacement during the catabolic neonatal period may potentially improve anabolism and weight gain. The use of exogenous insulin for optimising parenteral nutrition has received support of the American Academic of Pediatrics Nutrition Committee since 1985(19).

In addition to nutritional benefits, insulin therapy in the newborn may have other significant potential advantages. Improved glycemic control may help reduce the risk of sepsis(35). Moreover, insulin regulates levels of IGF1 and IGFBP1(55,56). Since IGF1 plays a role in fetal and postnatal brain growth and low IGF1 levels have been implicated in the pathogenesis of retinopathy of prematurity(57), insulin therapy may confer significant advantages.

The efficacy of insulin therapy to achieve glycemic control may be hindered by physical adsorption to the surface of the infusion containers and the tubing of the administration set. Utilisation of a standardised insulin delivery policy may enable better glycemic control. Although human albumin and polygeline (Hemaccel) have been used to reduce the adsorption of insulin, the potential risk of infection cannot be ignored. Alternative strategies have been explored and priming the extension tubing with insulin solution (1 unit/mL) by running (5 mL/hr) for 35-40 minutes before connecting to the infant maintains insulin concentrations within 90% of the initial concentration(58). However, it is pertinent that the efficacy of this strategy be confirmed in relation to devices currently used in neonatal intensive care units.

CONCLUSION

To conclude, the current data suggest that insulin therapy in hyperglycemic neonates may improve blood glucose control, caloric intake and weight gain. However, evidence from randomized controlled trials with adequate power is lacking. It is also not clear whether adequate short-term glycemic control in this setting confers any long-term advantage. Further, insulin may cause hypoglycemia and hypokalemia and have other significant long-term detrimental implications as it is closely related

to various growth factors. Insulin due to its anabolic and lipogenic activities(19) may also manipulate nutritional programming during a critical period and have long lasting implications in terms of obesity and vascular disease(59,60). It is, therefore, imperative that long term follow-up and safety studies be conducted in this field. Overzealous insulin therapy to optimise growth in non-hyperglycemic ELBW infants does not appear appropriate until the long-term safety of insulin has been confirmed in this population. Although the prospective NIRTURE study may answer some of these questions, the focus of the study design is on short term effects especially mortality. The control group are to receive standard neonatal care which in terms of hyperglycemia is very variable. Moreover, the study is not designed to assess other crucial aspects of this complex problem especially long term effects of hyperglycemia and insulin therapy. In view of the above and pending further research the following guideline is proposed (***Fig.* 1**).

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