

Effect of Enteral Administration of Insulin on Feeding Tolerance of Preterm Infants

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Abstract: The incidence of prematurity has risen drastically over the last twenty-five years. Premature deliveries are the leading cause of neonatal morbidity and mortality in the United States. One of the primary setbacks to establishing full enteral feeds in preterm infants is feeding intolerance. Certain bioactive substances and live cells in milk appear to influence neonatal gut maturation and growth through their transfer of developmental information to the newborn. The aim of the present study was to evaluate the effect of enteral administration of insulin in preterm infants born less than 32 weeks gestational age and weighing less than 1500 grams to determine whether enteral insulin supplement to the basic preterm formula enhances feeding tolerance or not. Also, to detect weight gain in infants after receiving enteral insulin compared to those not receiving enteral insulin. 50 of the preterm infants fulfilling the fore-mentioned criteria received 1 U/kg regular human insulin every six hours and other 50 of the preterm infant fulfilling the mentioned criteria were fed preterm milk formula without receiving regular human insulin and criteria of feeding intolerance will be monitored the Predictive Analytics Software (PASW Statistics version 18)., we found that feeding intolerance attacks are less frequent with preterm babies who received enteral insulin. Feeding intolerance is frequently encountered in the neonatal intensive care unit and the use of enteral insulin is a promising therapy that enhance GI development and reduce feed intolerance in preterm infants.

Keywords: Premature deliveries, neonatal gut maturation, human insulin.

INTRODUCTION

The incidence of prematurity has risen drastically over the last twenty-five years. Premature deliveries are the leading cause of neonatal morbidity and mortality in the United States. Preterm birth is defined as delivery before 37 weeks of gestation (AAP, 2007). Premature births account for over 12% of all live births in the United States, that is one in eight infants. Premature delivery is caused by multiple factors including preterm labor pain, premature rupture of membranes, and maternal or obstetric complications[1].

One of the many challenges in caring for a premature infant is providing adequate enteral nutrition. Because of the concerns for feeding intolerance and the development of necrotizing enterocolitis, many healthcare institutions have the current policy of nothing by mouth (NPO) for the first 24-48 hours. Numerous studies have shown that TPN

induces mucosal atrophy, which has been attributed to the absence of trophic signals released in response to luminal nutrients. However, the physiologic nature and relative importance of these trophic signals have not yet to be established [2]. Food deprivation for >24 h was shown to significantly decrease mucosal mass, but functional down regulation actually occurs within 12–18 h, which may be considered the maximal duration of food deprivation without enterally administered nutrients in normal life [3].

One of the primary setbacks to establishing full enteral feeds in preterm infants is feeding intolerance. Due to the previously mentioned defects in the GIT development and physiology in preterm infants. This presents clinically as residual feeds in the stomach prior to the next scheduled feeding, sometimes associated with abdominal distension, bile stained aspirates, or emesis. Consequences of feeding difficulties include withholding of feedings, reductions

in the amount of feeding, and the need for repeated abdominal radiographs to rule out the possibility that the feeding intolerance is related to necrotizing enterocolitis. In addition, the slow advancement of enteral feeding often leads to prolonged use of parenteral nutrition which predisposes these infants to nosocomial infections, hepatic dysfunction, and prolonged hospitalization⁽⁴⁾. Indeed, a relation exists between the time required to reach full enteral feedings and the duration of hospitalization[5].

Current therapeutic options for the management of feed intolerance in critically ill patients are the use of trophic or minimal EN feedings [6], slow advancement of feedings, the use of standardized feeding regimens, the use of breast milk for enteral nutrition, the use of specialized milk formula and prokinetic therapy such as erythromycin which is widely used to promote gastrointestinal motility via the motilin pathway, increasing proximal gut tone, enhancing the strength of intestinal contraction, and reducing pyloric outlet resistance. The use of probiotic administration has also been found to have a positive impact on the incidence of NEC [7].

Human milk also contains growth modulators, such as epidermal growth factor (EGF), nerve growth factor (NGF), insulin like growth factors (IGFs), and interleukins. Transforming growth factor (TGF)-alpha, TGF-beta, and granulocyte colony-stimulating factor (G-CSF) are also identified in human milk. These growth modulators are produced either by the epithelial cells of the mammary gland or by activated macrophages, lymphocytes (mainly T cells), or neutrophils in the milk. EGF and TGF-alpha were found at higher concentrations in the milk of mothers who delivered prematurely compared with those who delivered at term. EGF, TGF-alpha, and human milk stimulate fetal small intestinal cell proliferation *in vitro*, with the greatest increase in cell proliferation seen following exposure to human milk[8].

Certain bioactive substances and live cells in milk appear to influence neonatal gut maturation and growth through their transfer of developmental information to the newborn. Most of these bio substances have been identified in mother's milk in quantities that exceed maternal serum levels [8]. Data published on insulin levels in human and bovine milk show that mature milk contains about 50 mU/mL of insulin and colostrum concentrations are approximately 10 times higher [9]. Human milk insulin concentrations are similar in premature and full-term infants regardless of gestational age[10].

Insulin can interact with intestinal mucosa whether given orally or systemically, because its receptors are found on both the apical and basolateral enterocyte membranes. The positive effects of enteral insulin on gut maturation and mucosal enzyme

expression have so far been shown in suckling mice, suckling rats, and newborn piglets, pigs, and calves[11].

The aim of the present study was to evaluate the effect of enteral administration of insulin in preterm infants born less than 32 weeks gestational age and weighing less than 1500 grams to determine whether enteral insulin supplement to the basic preterm formula enhances feeding tolerance or not. Also, to detect weight gain in infants after receiving enteral insulin compared to those not receiving enteral insulin.

PATIENTS AND METHODS

A longitudinal prospective interventional hospital based study was conducted over the period from October 2011 to May 2012. The study included One hundred fifty preterm neonates born less than 32weeks gestational age and weighing less than 1500 grams admitted to the neonatal intensive care unit at Alexandria University Maternity Hospital

Inclusion Criteria

- Pre-term infants less than 32 weeks gestation.
- Birth weight less than 1500 grams.
- Postnatal age \leq 5 days.
- Fraction of inspired oxygen $<$ 0.60 at study entry.
- The infant is in a cardiovascular stable condition as regard heart rate, blood pressure, capillary refilling time, peripheral pulsation and arterial blood gas.

Patients with any of the following were excluded

- Major congenital malformation or Infants with genetic, metabolic or endocrine disorders.
- Maternal diabetes.
- The infant is treated with parenteral insulin
- Any diagnosis that necessitate NPO.
- Chest compression or any medication given to the infant during resuscitation

Patients with any of the following wer prematurely excluded from the study

- Infant developing necrotizing enterocolitis or, is suspected of having necrotizing enterocolitis during study period.
- Death of the preterm infant.

Patients were categorized into two groups

Group I: 50 of the preterm infants fulfilling the fore-mentioned criteria received 1 U/kg regular human insulin every six hours. The insulin was given through the nasoduodenal feeding tube after radiological confirmation, followed by the infant's usual feed. Insulin administration was started within 5 days of age and continued to 28 days of age or till discharge.

Group II: 50 of the preterm infant fulfilling the above mentioned criteria were fed preterm milk formula without receiving regular human insulin.

Intervention

Time of starting enteral insulin

Insulin administration was started within 5 days of age.

Duration of medication

Insulin administration was continued to 28th day of age or till discharge.

Medication protocol

Insulin was given through the nasoduodenal feeding tube after radiological confirmation, followed by the infant's usual feed.

Feeding protocol

Feeds were started in both groups of infants when they were clinically stable. The initial feeding volume was 10- 20 ml/kg/day and the volume of feeds was increased by that amount as tolerated until complete enteral feeding was achieved.

Monitoring

Criteria of feeding intolerance

Measures of feed intolerance were monitored throughout the hospital stay for both groups. For the insulin treated infants and the controls, decisions to withhold feeds because of feed intolerance were made by the attending doctor according to criteria listed below.

- Gastric residuals > 2ml/kg

- Gastric residuals > 50% of previous feeding.
- Abdominal distention.
- Coffee ground vomiting.
- Occult or gross blood in stool.
- Apnea and bradycardia
- Any of radiological signs of NEC.

Every baby in this study was evaluated as regard

- Duration of parenteral nutrition (PN) expressed in number of days
- Days to achieve full enteral feeds
- Age at full enteral feeds (days)

Assess weight gain in preterm infants

- Days to regain birth weight
- Duration of hospitalization expressed in total days since birth
- Weight gain expressed as g/kg/day at (7 days, 14days, 21 days & 28 days)
- Growth expressed as weight, length and head circumference percentile for gestational age, assessed at birth and at (7 days, 14days, 21 days & 28 days)

Effect of insulin on blood glucose

Measurement of blood glucose at 0, 30, and 90 minutes after the first, second, and fifth doses of insulin and every other day till discharge.

The results collected and analyzed using the Predictive Analytics Software (PASW Statistics version 18).

RESULTS

Table-1: Comparison between the two studied groups according to the number of bouts of feeding intolerance

	Insulin treated		Control	
	No	%	No	%
Number of bouts				
0	34	68.0	14	28.0
1	14	28.0	18	36.0
2	2	4.0	15	30.0
3	0	0.0	3	6.0
Min. – Max.	0.0 – 2.0		0.0 – 3.0	
Mean ± SD	0.36 ± 0.56		1.14 ± 0.90	
Median	0.0		1.0	
P	<0.001*			

p: p value for Mann Whitney test
 *: Statistically significant at p ≤ 0.05
 Group I: insulin treated group
 Group II: non- insulin treated group

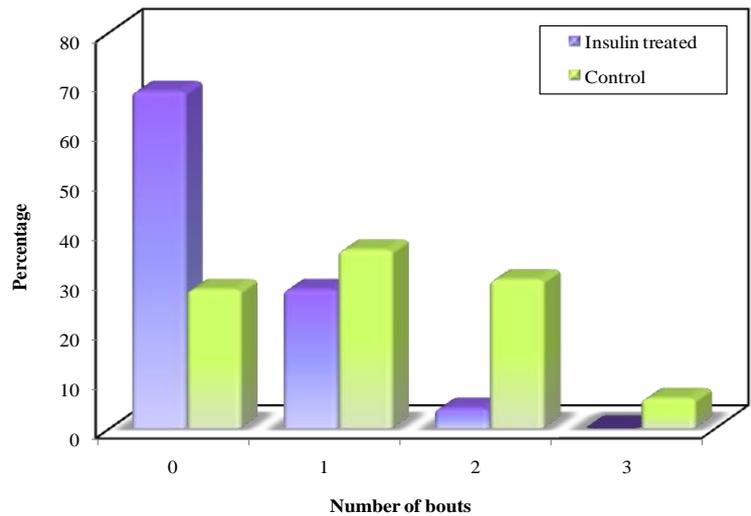


Fig-1: Comparison between the two studied groups according to the number of bouts of feeding intolerance

Table-2: Comparison between the two studied groups according to the criteria of feeding intolerance (cases had one attack)

	Insulin treated (n = 14)		Control (n = 18)		FEp
	No	%	No	%	
Gastric residuals					
>2ml/kg ->50%	14	100.0	18	100.0	-
Abdominal distention					
-ve	8	57.1	1	5.6	0.004*
+ve	6	42.9	17	94.4	
Coffee ground vomiting					
-ve	14	100.0	13	72.2	0.052
+ve	0	0.0	5	27.8	
Occult or gross blood in stool					
-ve	14	100.0	18	100.0	-
+ve	0	0.0	0	0.0	
Apnea and bradycardia					
-ve	14	100.0	17	94.4	1.000
+ve	0	0.0	1	5.6	
Radiological signs of NEC					
-ve	14	100.0	18	100.0	-
+ve	0	0.0	0	0.0	

FEp: p value for Fisher Exact test
 *: Statistically significant at $p \leq 0.05$

Table-3: Comparison between the two studied groups according to the criteria of feeding intolerance (cases had frequent attacks)

	Insulin treated (n = 2)		Control (n = 18)		FEp
	No	%	No	%	
Gastric residuals					
>2ml/kg ->50%	2	100.0	18	100.0	-
Abdominal distention					
-ve	2	100.0	5	27.8	0.111
+ve	0	0.0	13	72.2	
Coffee ground vomiting					
-ve	2	100.0	17	93.3	1.000
+ve	0	0.0	1	6.7	
Occult or gross blood in stool					
-ve	2	100.0	18	100.0	-
+ve	0	0.0	0	0.0	
Apnea and bradycardia					
-ve	2	100.0	18	100.0	-
+ve	0	0.0	0	0.0	
Radiological signs of NEC					
-ve	2	100.0	18	100.0	-
+ve	0	0.0	0	0.0	

FEp: p value for Fisher Exact test
 *: Statistically significant at $p \leq 0.05$

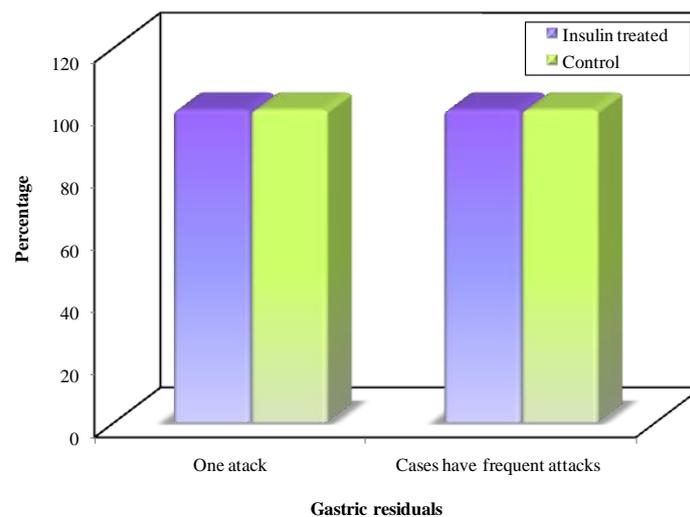


Fig-2: Comparison between the two studied groups according to the gastric residuals

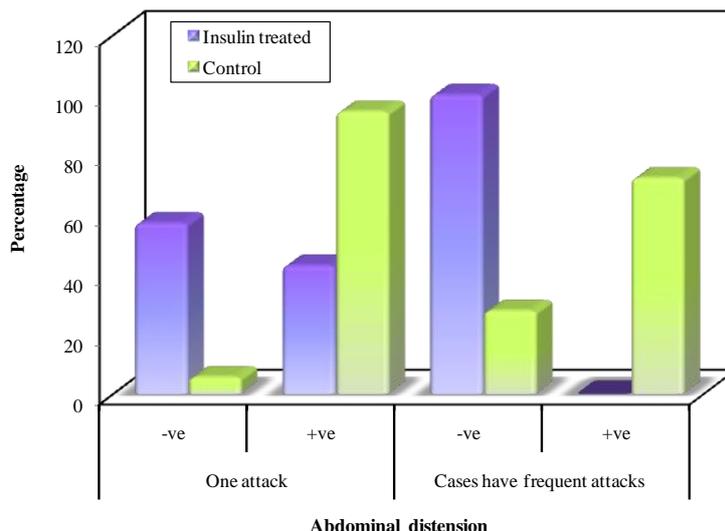


Fig-3: Comparison between the two studied groups according to the abdominal distention

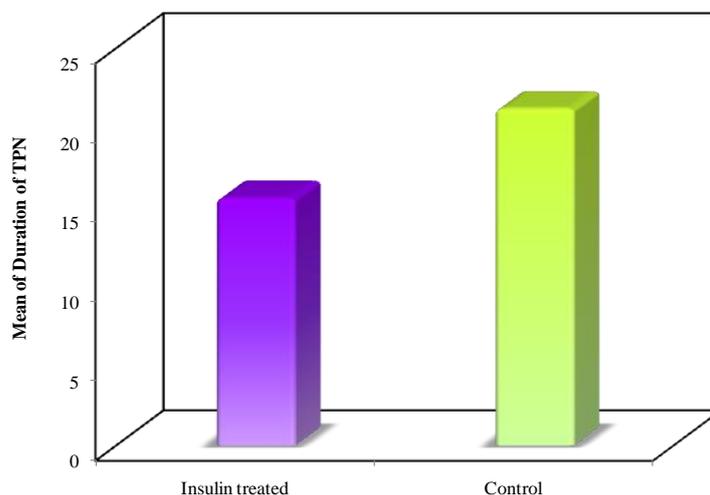


Fig-4: Comparison between the two studied groups according to the duration of TPN (days)

DISCUSSION

The present study showed no statistically significant differences between patients and controls regarding gestational age or postnatal age. All infants were cardiovascularly stable. The mean gestational age in patients group was 30.14 weeks and in the control group was 30.46 weeks.

Shulman study [12] the effects of enteral administration of insulin on preterm infants included 88 infants with a mean gestational age of patients of 27.8 ± 2.5 weeks and 27.8 ± 1.2 weeks for the control group, which are comparable to the present study. Birth weight in both studies was also comparable with a mean weight in the present study of 1067.9 gm for the patients which are comparable to 973 ± 310 gm in Shulman study.

Preterm infants with low gestational age are subjected to more morbidity and mortality mainly due to feeding intolerance compared to term infants who rarely experience feeding difficulties. Feeding intolerance is attributed mainly to the immaturity of the gastrointestinal tract[13].

The rationale for supplemental insulin for enteral feeding comes from the notion that it is normally present in human milk at high concentrations relative to maternal blood as was shown by Slebodziński *et al.*[14] It is not absorbed systemically to any significant degree as measured by changes in blood sugar in the present study and also in Shulman's study[12]. It is inexpensive and readily available. Overall this renders insulin as an attractive agent to enhance GI development in the preterm infant.

Earlier work on animal models showed the ability of insulin to enhance GI development and function. Shamir *et al.* [15] study the intestinal and systemic effects of oral insulin supplementation in rats after weaning, showed that oral insulin supplementation exerts intestinal trophic effects, as well as systemic effects in the postweaning period.

Similarly, Buts *et al.* [16] studied the responsiveness of villus and crypt cells to insulin during the suckling period. The authors demonstrated that the immature enterocyte of the suckling rat is responsive to insulin, whereas the mature enterocyte of the weaned rat is unresponsive.

Moreover, Albert *et al.* [17] studied the effect of insulin and other regulatory hormones on the suckling rat *juvenum* and reported that insulin caused an increase in lactase activity and induced early appearance of sucrose; however, it had no significant effect on morphology, or proliferation rate. Additionally, Arsenaull *et al.* [18] reported that insulin influences the maturation and proliferation of suckling mouse intestinal mucosa in organ cultures.

This study showed that duration of total parenteral nutrition (TPN) was significantly lower in insulin-treated infants than in control infants. Additionally, the age at full enteral feeds was significantly lower in insulin-treated infants. The days to regain birth weight were also significantly lower in insulin-treated infants.

Recently, Leaf *et al.* [19] reported in a randomized trial that included 404 infants randomly selected from 54 hospitals that early introduction of enteral feeds in growth-restricted preterm infants resulted in earlier achievement of full enteral feeding, shorter duration of TPN and does not appear to increase the risk of NEC.

Similarly, Kennedy *et al.* [20] in a systematic review in the Cochrane Database examined the concept of early versus delayed initiation of progressive enteral feedings for parenterally fed low birthweight or preterm infants. With a total of seventy-two babies. Early feeds were started on or before day four of life. Babies starting feeds earlier required less PN and had fewer episodes of suspected sepsis. There was no difference in the incidence of NEC, weight gain, conjugated jaundice or death.

Moreover, Denne SC [21] reported that enteral nutrition may be more effective than parenteral nutrition in limiting proteolysis and producing protein accretion in preterm infants, but the protein content of current preterm formulas may be inadequate for supporting optimal growth in this population.

The previous studies in addition to the study at hands agree that it is essential to start enteral nutrition early to preterm infants to ensure that metabolic homeostasis is kept stable and to limit postnatal growth retardation. Increasing feeding volumes to reach "full enteral feeding" is limited by individual feeding tolerance.

Lastly, although no side effects during the course of insulin administration or throughout the remainder of the hospital stay were observed, either in the present study or in Shulman's study [12], potential long term effects such as the development of insulin antibodies or the prevention of diabetes must be explored in future trials. Although the previously mentioned studies, either on animal model or human subjects, suggested that hypoglycaemia was unlikely to occur, a much larger number of infants would need to be studied to exclude the possibility.

CONCLUSIONS

From this study, we concluded that:

- Feeding intolerance is frequently encountered in the neonatal intensive care unit.
- The use of enteral insulin is a promising therapy that enhances GI development and reduces feed intolerance in preterm infants.
- Insulin is normally present in human milk at high concentrations relative to maternal blood. It is not absorbed systemically to any significant degree as measured by changes in blood glucose in this study.

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