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Hypophosphatemia in Refeeding Syndrome in Intrauterine Growth Restricted IUGR Neonates Who are Receiving Nutrition: A Prospective Observational Study

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Authors' contributions

This work was carried out in collaboration among all authors. Author JRG conceived the study. Authors JRG and VC designed the study. Authors VC and SAP carried out the study and did statistics. All authors did the literature search, helped write and approved the revisions and final draft.

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ABSTRACT

Objective: Electrolyte dysregulations particularly hypophosphatemia and hypokalemia following feeds in a starved person is known as refeeding syndrome, which may lead to life-threatening conditions like arrhythmias, heart failure, respiratory and neuromuscular compromise. To evaluate electrolyte dyscrasias following enteral or parenteral feeding, among intrauterine growth retardation (IUGR) neonates ie those who were starved in-utero, compared to non-IUGR neonates this study was planned.

Methodology: From March to August 2015, 60 IUGR and non-IUGR neonates who were admitted at birth before starting of nutrition, either by breast milk or electrolyte-free intravenous fluid. An infant was classified as IUGR when his birth weight was <10th percentile according to Fenton or Lubchenco growth charts. Venous blood was collected from intramural babies at zero hours of life or just before starting feeds to determine the basal level of serum electrolytes – phosphorus, magnesium and potassium, and was repeated in the following 48 and 72 hours.

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Results: There was no significant difference between the two groups based on sex, history of maternal pre-eclampsia and oligohydramnios. At 72 hours after the start of feeding, Hypophosphatemia was significantly more prevalent, in 33.33% of IUGR vs. 2% of the non-IUGR group, [RR-5, p = 0.010]. Hypokalemia 20% IUGR; 1% non-IUGR group, [RR-6, p = 0.103]. Hypomagnesemia 3% IUGR; 2% non-IUGR group, [RR-1.5, p = 0.640]. Combined electrolyte–hypophosphatemia with hypokalemia (6.6%) and hypophosphatemia with Hypomagnesemia (13.3%), were present only in the IUGR group. Hyperglycemia was not present in any neonate.
Conclusions: IUGR neonates are more likely to develop Refeeding syndrome when compared to non-IUGR babies, manifesting as decreased phosphorus, potassium and magnesium levels. Phosphorous should be a part of feeding nutrition in IUGR babies.

Keywords: Hypophosphatemia; IUGR; refeeding syndrome; neonates; hypokalemia; hypomagnesemia.

1. INTRODUCTION

Refeeding syndrome is a constellation of fluid and electrolyte dysregulations (hypophosphatemia, hypokalemia, Hypomagnesemia and hyperglycemia) that typically becomes apparent around three days following initiation of enteral or parenteral nutrition, after a period of malnutrition or starvation [1] either in-utero starvation or in the anorexic, intensive care unit, and post-surgical adult and pediatric population [2-4]. In chronic malnutrition, glucose and glycogen stores are

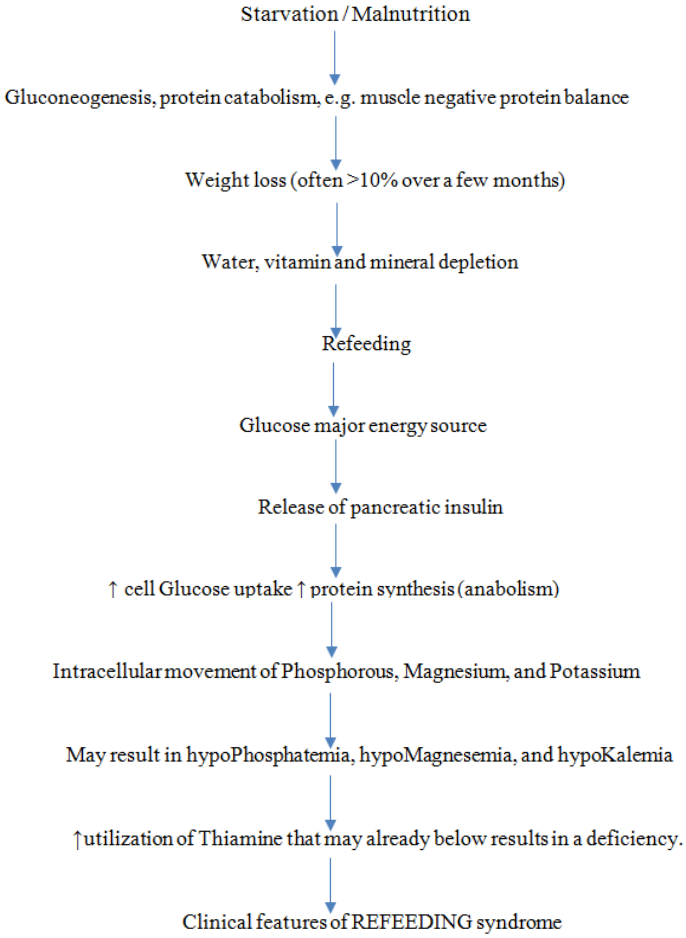

Fig. 1. Schematic diagram of some of the metabolic consequences of starvation and the refeeding syndrome [4]

depleted, followed by an adaptation in metabolism where energy is then derived from lipolysis and ketone production. Following the initiation of feeding, glucose metabolism results in increased phosphate usage for ATP production. This increased demand for electrolytes depletes serum stores of phosphorus and magnesium [1]. Hypophosphatemia is often accompanied by hypokalemia from intracellular shifts secondary to increased insulin [1]. Hyperglycemia may occur secondary to excess glucose delivery in a system now adapted to fat metabolism, and significant vitamin deficiencies, thiamine in particular (Fig. 1).

These physiologic disturbances, if untreated, can lead to life-threatening complications, including heart failure, arrhythmias, respiratory and neuromuscular compromise [5,6].

It is important to emphasize that the clinical features of the Refeeding syndrome can be seen after parenteral or enteral feeding. Indeed the key prerequisite is chronic nutritional deprivation regardless of the route of calorie administration. The degree of Refeeding is important in the aetiology of the condition. The duration of Refeeding also might be important, particularly if prolonged. Therefore, nutrition support may need to be modified over time by the patients' clinical conditions [7].

The true incidence of Refeeding syndrome is unknown —partly owing to the lack of a universally accepted definition. Early descriptions of Refeeding syndrome date back to World War II-era when starving prisoners of war experienced unexplained cardiac failure and peripheral oedema upon acute nutritional replenishment [8]. This phenomenon has been extensively described in the anorexic, intensive care unit, and post-surgical adult and pediatric population. In the neonatal population, intrauterine growth restriction (IUGR) secondary to placental insufficiency and altered oxygen delivery, results in a state of chronic, prolonged malnourishment that can be compared with that of the anorexic or critical surgical patient [9].

This study intends to evaluate the incidence of the characteristic electrolyte dysregulations in IUGR vs. non-IUGR babies following initiation of feeds – whether enteral or parenteral; and to report the occurrence of Refeeding syndrome if present, so that timely intervention and management of said disturbances can be implemented in decreasing hitherto unexplained or misidentified causes of perinatal morbidity and mortality.

2. METHODOLOGY

2.1 Research Design

This prospective study was conducted at a tertiary care hospital between March 2015 and August 2015. Study protocol was approved by the institutional review board and human ethics committee of the Government Medical College, Bhavnagar; in a consecutively enrolled cohort of neonates admitted to neonatal intensive care unit, in order to identify the biochemical responses of asymmetrical IUGR neonates from 30 to 40 weeks of gestation weighing more than 1 kg following the initiation of nutrition whether enteral or parenteral (Flowchart Fig. 2).

2.2 Inclusion Criteria

An infant was classified as IUGR based on the presence of neonatal criteria with a Birth weight less than the 10^{th} percentile on the Fenton or Lubchenco growth charts.

2.3 Exclusion Criteria

Congenital malformations, Genetic Diseases, Congenital infections, Symmetrical IUGR [Ponderal Index (weight gram/ length cm^3 x 100) of <2].

Detailed maternal history and clinical examination of the neonate were done. The weight of the baby was measured an electronic weighing scale. Classification of neonates was done according to gestational age as a term and preterm newborn based on New Ballard's scoring. The newborns were divided into small for gestational age (SGA) & appropriate for gestational age (AGA). Those with a birth weight of less than 10^{th} percentile for their gestational age were designated as small for gestational age based on the intrauterine growth charts by Fenton and Lubchenco. Length (cm), Head circumference (cm) was measured and ponderal index calculated for all. SGA group was included in the case group while the AGA group was considered as control.

Both IUGR and non-IUGR control groups were evaluated by collecting 2ml venous blood at zero hours of life or just before starting feeds, either breast milk or electrolyte-free intravenous fluid,

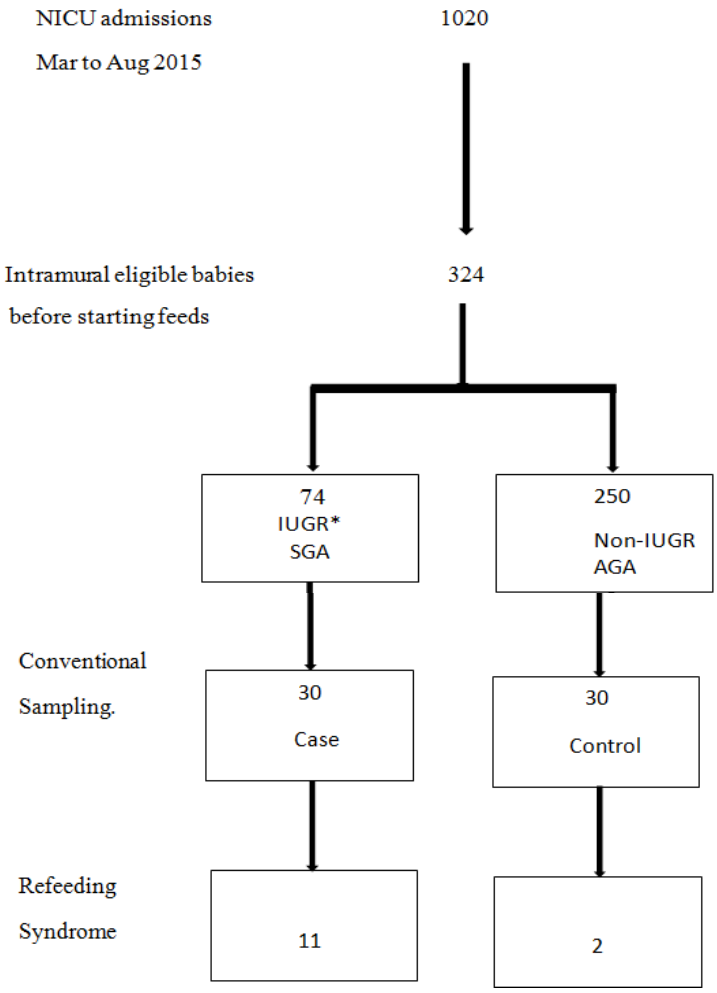

Fig. 2. Selection of study subjects and outcome

**Birth weight <10th percentile on the Fenton or Lubchenco growth charts in asymmetrical IUGR*

or mixed, to determine the initial level of Serum electrolytes – phosphorus, magnesium, and potassium together with (random) blood glucose measurement. No baby received formula feeds. The indication and type of feeds or fluids were similar for both groups. These measurements were repeated again after 48 and 72 hours of starting nutritional support. The cutoffs used to define the electrolyte dyscrasias to identify the Refeeding syndrome are listed in Table 1 [9].

2.4 Statistical Analysis

Data analysis was done by using Fisher's exact test for qualitative variables. Mann- Whitney test was used to see intergroup variations. A p-value < 0.05 was considered as significant. The Statistical software Graph pad instat3 was used for the analysis of the data and Microsoft Word and Excel have been used to generate graphs, tables etc.

Table 1. The cut-offs used to define the electrolyte dyscrasias [6]

Hypophosphatemia	S. phosphorus	< 4.0 mg/dl
Severe hypo-phosphatemia	S. phosphorus	<2.5 mg/dl
Hypokalemia	S. potassium	≤3.0 mg/dl
Hypomagnesemia	S. magnesium	<1.5 mg/dl
Hyperglycemia	plasma glucose	>180 mg/dl

3. RESULTS

A total of 1020 patients were admitted, out of which 324 patients were admitted on the first day of life before having received any form of nutrition; of these 74 were IUGR 14 were

excluded as a result of an unwillingness to participate in the study, dropouts, death before 3rd day of life, congenital anomalies and constitutional SGA status. The final sample size included 60 neonates from 30 to 40 weeks gestation (30 neonates in the IUGR group and 30 in the control – non - IUGR group by conventional sampling) and pre and post nutrition electrolyte levels were assessed as a part of the study in both the groups (Fig. 2).

Birth weight for study infants ranged from 1200 grams to 2500 grams. Neonates in the IUGR group had a birth weight group ranging from 1200 to 2200 grams while that in the non – IUGR group varied between 1300-2500 grams (Table 2). Neonates' gestational ages ranged from 30 weeks to 40 weeks. There were approximately equal neonates in the range of 32-34 weeks in both groups. However, there were more non-IUGR group neonates than IUGR in the lowest gestational age category. As there was no significant difference in terms of sex, maternal preeclampsia, and maternal oligohydramnios, these characteristics most likely did not influence study results. There was, however, a significant difference in terms of birth weight and gestational ages which are expected as IUGR is the differentiating feature between the two groups (Table 2).

Hypophosphatemia was found to be the most consistent finding among IUGR neonates following the initiation of feeds (Table 3). However, all three electrolyte deficiency together as a full spectrum of Refeeding syndrome, as well as Hyperglycemia (>180 mg/dl) was not observed in any subject. IUGR neonates were found to be more likely to develop refeeding syndrome as demonstrated by hypophos-phatemia – 33.33% incidence as compared to 2% in Non-IUGR group with a [RR- 5, 95% CI- 3.845, 0.263, p=0.010]. Hypokalemia was detected in 20% subjects in IUGR group and 1% in non-IUGR group [RR- 6, 95% CI- 3.947, 0.365, p=0.103]. Hypomagnesemia was detected in 3% of subjects in IUGR group and 2% in non-IUGR group [RR-1.5, 95% CI- 2.120, 1.310, p=0.640].

Combined electrolyte dyscrasias – hypophosphatemia with hypokalemia 6.6% IUGR and 1% Non-IUGR or hypophosphatemia with Hypomagnesemia had an incidence of 13.3% and 3.33% respectively, in the IUGR and non-IUGR group. No such results were obtained in a non –IUGR group (Table 3).

The mean and SD of IUGR and Non-IUGR group, in terms of significance, were as follows; phosphorous>potassium>magnesium>glucose (Table 4).

Thus hypophosphatemia was the most significant association with IUGR babies started on feeds. When comparing for *maternal* factors: Maternal history of *pre-eclampsia* was found in 11 neonates; 6 (20%) IUGR and 5 (16.6%) non-IUGR [RR- 1.1, 95% CI- 0.60, 2.05 p=1.00] and of whom only three subjects in IUGR group developed hypophosphatemia. In a similar fashion, of the total 60 neonates, eight were born to mothers having *oligohydramnios*; 4 (13%) IUGR and 3 (10%) non-IUGR [RR- 1.16, 95% CI- 0.57, 2.34, p = 1.00] and of whom only one subject in IUGR group developed hypophosphatemia.

Table 2. Demographic data of subjects (n = 60)

	Total n (%)	IUGR n=30(%)	Non IUGR n=30(%)	Statistical test	p value
Male	38 (63.3)	17 (56.6)	21 (70)	RR = 0.75	0.42
Female	22 (36.6)	13 (43.3)	9 (30)		
Birth weight (kg)					
Mean (SD)	1.79 (0.37)	1.63 (0.26)	1.96 (0.40)	U = 235.5	0.002
1-1.49	11 (18.3)	6 (20)	5 (16.6)		
1.5-1.99	29 (48.3)	18 (60)	11 (36.6)		
2.0-2.5	20 (33.3)	6 (20)	14 (46.6)		
Gestational age (weeks/days)					
30-31/6	5 (8.3)	0	5 (16.6)	U = 295	0.02
32-33/9	13 (21.6)	4 (13.3)	9 (30)		
34-35/9	21 (35)	13 (43.3)	8 (26.6)		
36-37/9	19 (31.6)	11 (36.6)	8 (26.6)		
38-39/9	1 (1.6)	1 (3.3)	0		
40-41/0	1 (1.6)	1 (3.3)	0		
Maternal preeclampsia	11(18.3)	6 (20)	5 (16.6)	RR =1.11	1.00
Maternal oligohydramnios	7 (11.6)	4 (13)	3 (10)	RR =1.16	1.00

RR – Relative risk; U – Mann Whitney test

Table 3. Electrolyte changes after 72 hours

Incidence	IUGR n = 30	Non-IUGR n = 30	p-value	Relative risk (95% CI)
HyPh*	10 (33.3%)	2 (6.6%)	*0.010*	5 (3.845, 0.263)
HyK	6 (20%)	1 (3.3%)	0.103	6 (3.947, 0.365)
HyPh + HyK*	2 (6.6%)	1 (3.3%)	*0.021*	2 (3.845, 1.653)
HyMg	3 (10%)	2 (6.6%)	0.640	1.5 (2.120, 1.310)
HyPh + HyMg	4 (13.3%)	1 (3.3%)	0.161	3.9 (2.448, 0.272)

**HyPh = Hypophosphatemia< 4.0 mg/dl (severe hypophosphatemia < 2.5 mg/dl not observed in any neonate), HyK = Hypokalemia< 3.0 mg/dl, HyMg = Hypomagnesemia < 1.5 mg/dl*

Table 4. Mean / SD of each electrolyte in both groups in mg/dl

	Non IUGR Mean/SD	IUGR Mean/SD	p-value
Phosphorous	5.146/ 0.93	3.936/ 0.45	*0.001*
Potassium	5.236/ 1.00	4.319/ 1.31	*0.02*
Magnesium	1.786/ 0.23	1.796/ 0.39	*0.046*
Glucose	63.93/ 7.96	77.55/ 8.54	0.054

IUGR - Intra uterine growth retardation; SD - Standard deviation

4. DISCUSSION

In this cohort of 60 neonates, IUGR babies presented higher rates of hypophosphatemia either associated with hypokalemia or Hypomagnesemia; which are laboratory markers of Refeeding syndrome. This association with IUGR status supports the hypothesis of Refeeding syndrome occurring in this population. However, a combined spectrum of all three electrolyte abnormalities (and) with hyperglycemia was not found in any of the study subjects.

An animal study linking hypophosphatemia to growth restriction found that IUGR piglets fed high-protein formula had poor growth and hypotonia, with associated hypophosphatemia and hypokalemia [10]. However, the only human study depicting any clinical evidence of occurrence of Refeeding syndrome in the neonatal population was a *retrospective* cohort study, performed at Division of Neonatology, Medical University of South Carolina Children's Hospital, Charleston, USA wherein VLBW infants admitted over a 10-year period (271 IUGR and 1982 non-IUGR) were evaluated for specific electrolyte abnormalities in the first postnatal week [9].

In our study, which is the first prospective study of its kind, the incidence of hypophosphatemia was 33.33% (10) in neonates in the IUGR group and 2% (2) in the non- IUGR group [RR- 5, 95% CI- 3.845, 0.263, p=0.010], Hypokalemia was detected in 20% subjects in IUGR group and 1% in non-IUGR group [RR- 6, 95% CI- 3.947, 0.365, p=0.103], Hypomagnesemia was detected in 3% subjects in IUGR group and 2% in non-IUGR with [RR-1.5, 95% CI- 2.120, 1.310, p=0.640]. Comparative results by Ross and Finch were- Hypomagnesemia in 4.8% and 0.5% of IUGR and non-IUGR groups respectively with an (RR-9.94, 95% CI 4.31, 22.89).

In the present study, only two subjects (6.6%) in the IUGR group and one in the non-IUGR group (1%) developed a combination of hypophosphatemia with hypokalemia as compared to 20% and 2.7% subjects in IUGR and non-IUGR group respectively in the study by Ross and Finch.

Similarly, the combination of hypophosphatemia with Hypomagnesemia was also noted only in the IUGR group with 13.33% incidence in our study; however, the study by Ross and Finch demonstrated an incidence of 4.43% and 0.15% in IUGR and non-IUGR groups.

No subject developed hyperglycemia during the study duration. So the same cannot be compared with the findings of hyperglycemia detected by Ross and Finch [9] at 2.2% and 0.5% in IUGR and non-IUGR groups. Hyperglycemia was not observed in our study because of frequent glucose monitoring and tighter control. No difference was noted in both the studies based on sex. While the study by Ross and Finch depicted a reasonable association between pregnancy-induced hypertension and hypophosphatemia, no such association was discovered in our study. We also studied the effect of maternal oligohydramnios; 13% and 10% respectively in IUGR and the non-IUGR group had a history of maternal oligohydramnios and only one subject in IUGR group developed hypophosphatemia. There was no statistically significant difference. As this parameter was not

studied by Ross and Finch, it cannot be compared.

5. CONCLUSION

The difference in the incidence of various electrolyte disturbances could be attributed to the difference in basic study design. However, findings from both studies suggest that the possibility of Refeeding syndrome does exist in the neonatal population; with hypophosphatemia being the significant and consistent electrolyte abnormality associated with it and thus may contribute to perinatal morbidity. IUGR neonates are more likely to develop Refeeding syndrome when compared to non-IUGR babies, manifesting as decreased phosphorus, potassium and magnesium levels.

6. RECOMMENDATION

Phosphorous should be a part of feeding nutrition in IUGR babies. Monitoring of electrolytes, especially phosphorus, following initiation of parenteral or enteral nutrition in IUGR neonates should be protocoled. A similar study on Extreme LBW neonates (weighing less than 1 kg) should be conducted.

CONSENT AND ETHICAL APPROVAL

College Ethics and Scientific committee/ Institutional Review Board (IRB) approved the study. Appropriate written consent was obtained from parents.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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