# FREQUENCY, RISK FACTORS, TREATMENT AND OUTCOMES OF HYPERINSULINEMIC HYPOGLYCEMIA IN NEONATES PRESENTING WITH PROLONGED HYPOGLYCEMIA IN A TERTIARY CARE HOSPITAL OF KARACHI, PAKISTAN

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## ABSTRACT

***Objective:*** To identify frequency of hyperinsulinemic hypoglycemia in neonates with prolonged hypoglycemia, its risk factors, treatment and outcome.

***Study Design:*** Cross-sectional analytical study.

***Place and Duration of Study:*** The department of Pediatrics, neonatal unit of a tertiary care hospital, from Jan 2014 to Dec 2018.

***Methodology:*** Data on infants with prolonged hypoglycemia was collected retrospectively from hospital medical records. Cases of Hyperinsulinemic hypoglycemia were analyzed for demographic characteristics, associated risk factors, and details of time and age of diagnosis along with the management.

***Results:*** Fifty two cases (50.9%) were studied and treated for Hyperinsulinemic hypoglycemia out of 102 with prolong hypoglycemia. Male gender, Pregnancy induced hypertension, maternal diabetes and Small for gestational age were common risk factors associated with hyperinsulinemic hypoglycemia ($p$<0.05). Mean days taken to maintain normoglycemia on feed and medicine (off IV) was 7.7 ± 3.3, while total duration of medicine required for normoglycemia on feed only was 23.5 ± 2.0 days. Overall 48 cases (92%) were cured, 29 (56%) patients were treated with diazoxide, whereas 3 (6.0%) cases were lost to follow up in outpatient department and 1 (2.0%) patient died.

***Conclusion:*** Hyperinsulinemia remains a common cause of prolonged hypoglycemia in neonates. Male gender, Pregnancy induced hypertension, diabetes, and Small for gestational age are associated risk factors. Diazoxide is a safe and effective therapy.

**Keywords:** Glucose Infusion Rate, Hyperinsulinemic hypoglycemia, Prolonged hypoglycemia, Small for gestational age (SGA).



## INTRODUCTION

Hypoglycemia is a most prevalent metabolic disorder found in newborn infants[1]. Hypoglycemia during first 48 Hours is considered to be a transient phenomenon in a normal newborn infant having no major clinical implications[2,3]. It is very important to differentiate this normal physiologic transition from the disorders that result in persistent hypoglycemia which persists or present for the first time beyond the first 48 hours of life or requiring parenteral glucose infusion to maintain euglycemia[4]. This consequential form of hypoglycemia caries high risk of serious neurologic implications and necessitate prompt diagnosis and effective management to avoid long term morbidities[3].

Hyperinsulinism is the major cause of prolonged hypoglycemia in neonates and is biochemically characterized by inappropriate secretion of insulin in the presence of hypoglycemia in infants >48 h of life receiving a glucose infusion rate (GIR) of >8 mg/kg/min along with Hypoketonemia, hypofattyacidemia, and a positive glycemic response to glucagon during hypoglycemic state (table-I).

Hyperinsulinemic Hypoglycemia (HIH) can be sub classified into three clinical forms i.e. transient, prolonged, and persistent (congenital) form. Transient HIH usually resolves within days

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following increment of feeds or short-term glucose infusion. Prolonged HIH characteristically require high GIR to maintain euglycemia and demonstrate diazoxide responsiveness where resolution is observed in weeks to months. Persistent HIH is often found in genetic forms of pancreatic ß-cell disorders which can be focal, diffuse, or atypical based on their histological characteristics. In a study[5-10]

Prolong neonatal hyperinsulinism is much more common than genetic forms of hypoglycemia and often associated with risk factors including small for gestational age (SGA), Infant of diabetic mothers (IDM), perinatal stresses, prematurity, maternal hypertension[11]. The clinical severity and duration of hyperinsulinism in infants with prolong neonatal hyperinsulinism is variable and can't be predicted by the degree of perinatal stress.

Diazoxide, an insulin hormone suppressant, is considered to be the first line therapy for HIH in neonates and has a good safety profile and should be tried before considering genetic work up[12-14]. Therefore; its early use especially in SGA infants with HIH, helps in faster hypoglycemic control and reduces the risk of sepsis even in low doses 3mg/kg/day[15].

Knowing the fact of insufficient research data from under developed countries, with respect to recognition, diagnosis and management of hypoglycemia, this study was conducted at JCI accredited, tertiary care hospital of Pakistan, with the objective to determine the frequency of hyperinsulinemic hypoglycemia, its risk factors, treatment and short term outcome in neonates presented to our unit with Prolonged hypoglycemia over the last 5 years. This study will pave forward to establish and implement standardized protocol prospectively on the case management of hypoglycemia and in particular HIH cases.

## METHODOLOGY

A study was carried out from January 2014 to December 2018 at a level III neonatal unit in a tertiary care hospital of Karachi, Pakistan. Institutional Ethics Review board (IERB) permission was taken, certificate number being 2019-1121-3669. All the infants admitted during above mentioned time frame, fulfilling the criteria, i.e. neonates (from day 3 to day 28) who presented with prolonged hypoglycemia were enrolled for the study through universal sampling method. The neonates with suspected or diagnosed inborn error of metabolism, sepsis, endocrine causes, necrotizing entercolitis or not being fed due to their clinical condition were excluded. The enrolled neonates data was collected for demographic characteristics, antenatal and birth history, maternal co morbidity, any factor associated with hyperinsulinemic hypoglycemia in the mother and baby, maximum GIR required to maintain euglycemia, and laboratory investigation like Urinary ketones, Insulin Level and Random Blood Sugar (RBS) were recorded on specific proforma. The data regarding time and age of diagnosis with the medical management given to correct hypoglycemia was collected in a very concise way for the study. Outcome was determined by calculating the duration of pharmacologic treatment and days to become euglycemic without any Pharmacologic support. We also performed a 6 month follow up after discharge to assess the clinical status, need of pharmacologic support to maintain normoglycemia and the possible drug side effects if any. The collected data was analyzed through SPSS version 22 and presented in tables. T-test was used to assess the difference in average days of hospital stay between levels of insulin, GIR and additional drug required.

## RESULTS

During the study period,total 652 cases of neonatal hypoglycemia cases were diagnosed. Out of which 102 cases of prolonged hypoglycemia were selected whereas remaining 550 cases were transient hypoglycemia cases. Out of 102 cases, 52 cases were finally selected, that were fulfilling the inclusion criteria of the study and labeled as HIH. The Frequency of HIH among patients with prolonged hypoglycemia was 52 (50.9%), while the overall frequency of HIH in neonatal hypoglycemia was 52 (7.9%).

Majority of neonates 46 (88.0%) were males with mean gestational age of 36.5 ± 1.5 weeks. Place of delivery for 27 (52%) neonates was the same tertiary care hospital whereas remaining was born in other hospitals/ cities. Overall 45 cases (86.5%) were delivered through Cesarean section. Onset of hypoglycemia was found in <2 days in majority of the newborn 36 (69%). Major clinical symptoms were poor sucking and lethargy (table-II).

**Table-I: Diagnostic criteria for hyperinsulinemic hypoglycemia.**

| |
|---|
| Glucose infusion rate of >8 mg/kg/min to maintain plasma glucose ≥ 60mg/dl in infants >48 hour of life |
| Inappropriate insulin levels when plasma glucose <60mg/dl (insulin >1.6 mU/L) |
| *Hypoketonemia -<0.6 mmol/L |
| **Hypofattyacidemia -<0.5 mmol/L |
| **Glucagon stimulation test |
| When plasma glucose level <60mg/dl |
| Give glucagon 1 mg IM/IV |
| Check plasma glucose every 10 min. A rise of >1.5 mmol/L within 20 min supports a diagnosis of hyperinsulinemic hypoglycemia |

**We used absent urinary ketones, **We didn't use these criteria for the diagnosis of HIH.*

**Table-II: Demographic characteristics and clinical manifestation in neonates with HIH.**

| S. No | Characteristic | n (%) |
|---|---|---|
| 1. | **Gender** | |
| | Male | 46 (88%) |
| 2. | Gestational age (weeks) Mean ± SD | 36.5 ± 1.5 |
| 3. | **Gestation** | |
| | Term | 29 (56%) |
| | Preterm | 23 (44%) |
| 4. | Weight (kg) Mean Weight ± SD | 2.4 ± 0.8 |
| 5. | **Place of Delivery** | |
| | Inborn | 27 (52) |
| 6. | **Mode of Delivery** | |
| | Lower segment cesarian section | 45 (86.53) |
| | Spontaneous vaginal delivery | 07 (13) |
| 7. | **Onset of Hypoglycemia** | |
| | < 2 Days | 36 (69) |
| | 3-7 days | 07 (14) |
| | >7 days | 09 (17) |
| 8. | Onset of hypoglycemia (Days) Mean ± SD | 3.7 ± 5.5 |
| 9. | **Clinical Symptoms (Multiple Choice)** | |
| | Poor sucking | 30 (58) |
| | Lethargy | 19 (37) |
| | Jitteriness | 02 (04) |
| | Seizures | 01 (02) |
| | Hypotonia | 01 (02) |
| | None | 07 (13) |

Data was analyzed to determine the association between the risk factors and development of HIH using Pearson chi square test and Fisher's exact test. According to the findings, babies born to mothers having pregnancy induced hypertension (PIH) and diabetes were found to be more hypoglycemic with hyperinsulinemia (HIH) and showed a statistical significant difference at $p<0.05$ in HIH and Non HIH cases. However, babies born to mothers having pre eclampsia did not show HIH with any statistical significance.

**Table-III: Association between risk factors and hyperinsulinemic hypoglycemia.**

| | Hyperinsulinemic Hypoglycemia | Non-Hyperinsulinemic Hypoglycemia | *p*-value |
|---|---|---|---|
| **Maternal** | n=52 | n=50 | |
| **PIH** | | | |
| Yes | 24 (46%) | 9 (18%) | 0.002†* |
| **Diabetic** | | | |
| Yes | 7 (13%) | - | 0.013* |
| **Preeclampsia** | | | |
| Yes | 4 (8%) | - | 0.12ǂ |
| **Fetal** | | | |
| **Evidence of Fetal Distress** | | | |
| Yes | 5 (10%) | 2 (4%) | 0.44ǂ |
| **Intrauterine Growth** | | | |
| SGA | 31 (56.9%) | 11 (22%) | <0.001ǂ** |
| AGA | 17 (33%) | 39 (78%) | |
| LGA | 4 (8%) | - | |

**p-value<0.05, **p-value<0.0001, †Pearson Chi Square test, ǂFisher's Exact test*

Similarly, Small for gestation age (SGA) babies, were observed to develop HIH and thus showed statistical significant difference between HIH and Non HIH cases, whereas evidence of fetal distress was not found to show any statistical significant difference in our study (table-III).

Majority 36 (69%) of the neonates were treated with central line once shown HIH , mode of feed was cup and spoon 34 (65%) and formula milk was given for correction of hypoglycemia in

49 (94%) of the cases. Diazoxide was the main drug which was used in 29 (56%) cases whereas octreotide and steroid was given to one neonate each. Surgical intervention was not offered to any neonate. Our data shows that number of days taken to get a neonate off IV dextrose and maintain normoglycemia on oral feed with pharmacologic treatment were 7.7 ± 3.3 days, whereas mean number of days from start of pharmacologic treatment to off IV dextrose were 5.5 ± 3.4

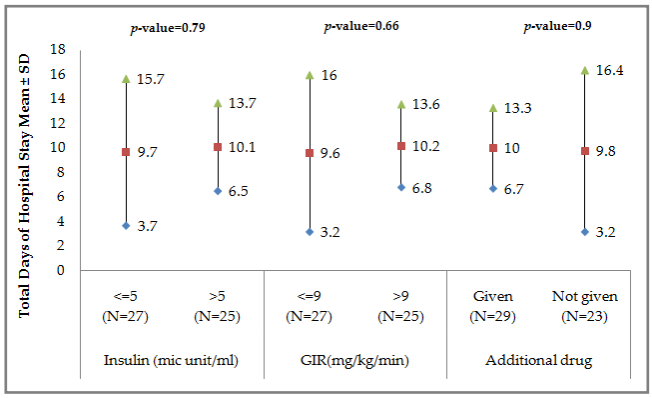


**Figure: Comparison of hospital stay (Days) with insulin level, GIR and drug effects.**

*T-test were used to assess the difference in average days of hospital stay between 2 levels of Insulin, GIR and Additional drug. However there was no significant difference between the levels of each variable, (p-value = 0.79, 0.66 and 0.9 respectively)*

days. Similarly mean number of days of initiation of pharmacologic treatment was 3.9 ± 2.0 in babies with HIH. Mean hospital stay for management of HIH, was 9.9 ± 5.0 days whereas the total duration of pharmacologic therapy required to maintain normoglycemia on oral feeds only was 23.5 ± 2.0 days. Medication therapy was started in 15 cases within 3 days whereas in 14 cases it was started from 4-8th day. In our study, Diazoxide was the most commonly used medication that was given to majority of neonates with HIH 29 (56%). It was given for up to 7 days in 4 neonates, 8-30 days in 18 neonates and 31-60 days in 5 cases till maintenance of euglycemia and achieving full oral feeds. No major diazoxide induced side effect was observed.

The hospital stay of the babies was further compared with insulin levels, GIR and Additional drug effect in recovery but these were found to have no statistical significance (figure).

Regarding outcome of the study, 49 cases (94%) were followed up in the clinic for 6 months. 48 cases (92%) were cured whereas 3 (6.0%) cases were lost to follow up in OPD and 1 (2.0%) case was expired (table-IV).

**Table-IV: Treatment and outcome of patients with HIH.**

| Treatment | n (%) |
|---|---|
| **Type of Treatment** | |
| Central line | 36 (69) |
| Peripheral line | 16 (31) |
| **Mode of Feed** | |
| Cup and Spoon | 34 (65) |
| OG feed | 18 (35) |
| **Type of Feed** | |
| Breast feed | 03 (06) |
| Formula feed | 49 (94) |
| Max GIR (mg/kg/min) | 10.0 ± 2.5 |
| Diazoxide | 29 (56) |
| Octeriotide | 1 (02) |
| Steroid | 1 (02) |
| Surgical intervention | - |
| **Outcome** | **Mean ± SD** |
| Mean number of days taken to get off IV dextrose and maintain normoglycemia on oral feed with pharmacologic treatment | 7.7 ± 3.3 |
| Mean number of days from start of pharmacologic treatment to off IV dextrose | 5.5 ± 3.4 |
| Mean number of day of initiation of pharmacologic treatment | 3.9 ± 2.0 |
| Mean hospital stay (days) for management of HIH | 9.9 ± 5.0 |
| Total duration of pharmacologic therapy required to maintain normoglycemia on oral feed only | 23.5 ± 2.0 |
| **Follow up** | |
| Yes | 49 (94) |
| Lost to follow up | 03 (06) |
| **Outcome** | |
| Cured | 48 (92) |
| Expired | 01 (2) |
| Lost to follow up | 03 (6) |

## DISCUSSION

Neonatal hypoglycemia is a threatening condition due to its complication especially the neurological deficit. However, its complications could be preventable with simple measurements.

There was significant increase in the number of infants enrolled with prolong hypoglycemia once we updated and implemented our institutional guidelines on management of Neonatal hypoglycemia in NICU. Therefore, the neonatologist needs to identify at-risk babies and enroll them into a pathway that ensures safe, physiological transition to extra uterine life.

According to a study Chandran *et al*[5] the management of infants at risk of hypoglycemia, which begins in the first hours to days of life with the potential to lead to a diagnosis of HH, is of fundamental interest to doctors looking after newborn babies. Our study results are same as we have treated them at very early stage of the diagnosis.

In our study males were 88% which showed that male gender is a dominating risk factor for hypoglycemia and this observation was also previously published by Skovrlj[16] and Amanda *et al*[17]. The mean birth weight noted in our study was lowered as compared with the western literature and was 2400.0 ± 800.0 g that depicts the quality of maternal nutrition and newborn growth in developing countries and associated postnatal complications of hypoglycemia. According to a study Amanda *et al*[17], mean birth weight of the whole cases was 3155.70 ± 847.70g, which is significantly higher than the findings of current study. More over 61.7% were full term with mean gestational age 38.52 ± 1.71weeks. Our study results were quite similar with full term neonates 56.0% and gestational age 36.5 ± 1.5 weeks.

In a study[16] conducted in Turkey the frequency of neonatal HIH was 9.18%, that was also comparable with our figures of 7.98%. Moreover our study also endorsed that this frequency is almost 6 times higher in neonates presented with prolong hypoglycemia, raising the percentage to 50.9%. We also noted that small for gestational age babies (SGA) required long duration of stay to become euglycemic and that was endorsed with similar figures by Amanda *et al*[17] conducted in Turkey. As discussed earlier the pharmacologic therapy used in our study was diazoxide in 56% of neonates who did not respond to first line management with a mean duration of treatment of 23.5 ± 2.0 days. These findings correlate well with the study conducted by Skovrlj *et al*[16], showing that the diazoxide treatment was utilized in roughly half (29/52 to 56%) with a median duration of treatment for 91 days.

In a study[18] Louvain *et al* that showed that maternal weight gain, C-section, gender, consumption of fresh cooked vegetables, fresh fruits and fruit juices, low fat dairy products, light fat products, and daily bread were significantly associated with hyperinsulinism. Maternal body mass index, hypertension, gestational diabetes, birth weight percentile, gestational age and 5-minute Apgar score were not related to HIH. In our study gender, PIH, diabetics and SGA was found significantly associated with Hyperinsulinism whereas preeclampsia and fetal distress did not find any statistical association with the hyperinsulinism.

## LIMITATION OF STUDY

This study has a limitation that it was based on single hospital with only last five years data. The result of a large sample size study with major public and private tertiary care hospital may be different but the management strategies and treatment outcome may remain the same.

## RECOMMENDATION

Pediatrician should be trained in diagnosis of prolong HIH and the immediate actions taken to save the lives of neonates under their supervision with proper dose and management procedure. A universal protocol and its timely implementation are highly recommended for the same. We also recommend a multi-center study with large sample size including major public and private tertiary care hospitals to validate our results.

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## CONCLUSION

Hypoglycemia is the most common metabolic problem in neonates. Prolong hypoglycemia, can be a serious form of it, and can lead to a consequential neurodevelopmental outcome if not managed timely. The management of neonatesat risk of prolong hypoglycemia, begins in the initial first hours to days of life with the potential underlying diagnosis of HIH. We suggest that the early diagnosis and management is a better option for neonates with hyperinsulinemic hypoglycemia and medical management with diazoxide alone is an effective and safe approach.

## CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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