# IS HYPERGLYCEMIA A RISK FACTOR FOR NEONATAL MORBIDITY AND MORTALITY?

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## ABSTRACT

***Objective:*** To determine the extent of morbidity and mortality in newborns with neonatal hyperglycemia where published data are limited.

***Study Design:*** Observational case control study.

***Place and Duration of Study:*** Department of Neonatology, the Children's Hospital and the Institute of Child Health Lahore, from 1st May to 31st Oct 2015.

***Material and Methods:*** A prospective, observational case control study was conducted in the Department of Neonatology, the Children's Hospital and the Institute of Child Health, Lahore, from 1st May till 31st October 2015. The sample size was 192, with 96 babies each in 'study' and 'control' groups. All neonates fulfilling the inclusion criteria were enrolled in the 'study group' while 'control group' consisted of euglycemic babies matched for age, weight, gestational age and clinical status. All babies were monitored for morbidity intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), infections and outcome (duration of hospital stay, discharged or expired).

***Results:*** The data analysis showed that 74% neonates, of study group, had hyperglycemia during first week of their lives. Moreover, 84.4% babies were less than 2.5kg. Significant high number of babies in the study group developed complications ($p$<0.001). These complications included IVH ($p$<0.001), NEC ($p$=0.024) and infections ($p$=0.019). As regards outcome, the neonates in the study group had significantly prolonged hospital stay ($p$=0.028), lower discharge rate ($p$=0.040) and higher mortality ($p$=0.040).

***Conclusion:*** Hyperglycemia not only significantly increases risk of IVH, NEC and infections, but also prolongs hospital stay and contributes to mortality among newborns.

**Keywords:** Hyperglycemia, Morbidity, Outcome.



## INTRODUCTION

Neonatal hyperglycemia is one of the commonly encountered metabolic abnormalities in sick neonates. It has been defined variably but generally accepted level for diagnosing hyperglycemia is blood glucose level >125 mg/dl (6.9 mmol/L) or serum glucose concentration ≥150 mg/dl (8.3 mmol/L), regardless of gestational age[1]. However, indication for intervention is either two consecutive blood glucose levels >252 mg/dl (14 mmol/L), checked at least 2 hours apart, or even single reading of >216 mg/dl (12 mmol/L) with glycosuria[2].

The first week of life, especially early 3 to 5 days, is most vulnerable period for development of neonatal hyperglycemia[3]. Moreover, it has indirect relationship with birth weight and gestational age[3,4]. Incidence of hyperglycemia is 72% in babies weighing <1000gm as compared to ≤5% in babies of >2500gm[5]. Other risk factors include prematurity, intrauterine growth retardation (IUGR), birth asphyxia, stress, intravenous lipid infusion, high rate of infusion of glucose, absence of enteral feeding and drugs (theophylline, dopamine, steroids, β2 agonists, phenytoin[6,7]).

The pathophysiology includes increased endogenous glucose production, hypo-insulinemia, insulin receptor insensitivity or resistance, catecholamine and other similar anti-insulin hormones. Hyperglycemia may be incidental finding or can present with symptoms

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like dehydration, fever, failure to thrive[3]. In addition, hyperglycemia can be the first presentation of neonatal diabetes mellitus[8].

Different studies have shown varied relationship of neonatal hyperglycemia with intra-ventricular hemorrhage, late onset infections, necrotizing enterocolitis and prolonged length of hospital stay[9-12]. Many studies have been conducted on this aspect in developed countries but these show variable correlation between neonatal hyperglycemia and consequential morbidity (IVH, NEC and infections) and outcome (hospital stay, discharge and expiry). Moreover, published data in developing countries like Pakistan are limited. The current study has been designed with an aim to fill in this gap and to determine the extent of morbidity and mortality in our set- up.

## MATERIAL AND METHODS

A prospective, observational case control study was conducted in the Department of Neonatology, the Children's Hospital and the Institute of Child Health, Lahore, from 1st May 2015 till 31st October 2015. Babies were enrolled in the study after getting ethical approval from Intitutional Review Board (IRB) and informed consent from parents.

The sample size was calculated to be 192, where 96 babies were required each in 'study' and 'control' groups and was calculated with 95% confidence level, 10% margin of error and 5% level of significance by taking average percentage of hyperglycemia as 50%. It was done by using formula;

$$n = \frac{z^2 (p) (1-p)}{d^2}$$

Total of 192 babies were selected using non-probability, purposive sampling technique. All neonates, who had at least two readings of blood sugar taken 2 hours apart in hyperglycemic range, were included in the 'study group' while 'control group' consisted of euglycemic babies matched for age, weight, gestational age and clinical status. Patients were managed as per standard guidelines. While all those babies were excluded that had incomplete data, lack of consent from parents and congenital malformations.

All babies were monitored for morbidity (IVH, NEC and infections) and the outcome was measured as duration of hospital stay, discharged or expired. The data were recorded using a proforma and analyzed using SPSS v20. The studied variables have been described by counts

**Table: Demographic data of study participants.**

| Parameter | | Study n(%) | Control n(%) | Odd ratio | 95% confidence interval | *p*-value |
|---|---|---|---|---|---|---|
| Gender | Male | 62 (64.5) | 64 (66.67) | 0.916 | 0.504 – 1.664 | 0.761 |
| | Female | 34 (35.5) | 32 (33.33) | | | |
| Weight (kg) | ≤ 1.5 | 46 (48) | 48 (50) | 1.023 | 0.824 – 1.270 | 0.256 |
| | 1.6 – 2.0 | 20 (21) | 13 (13.5) | | | |
| | 2.1 – 2.5 | 15 (15.6) | 23 (24) | | | |
| | 2.6 – 3.0 | 11 (11.4) | 10 (10.4) | | | |
| | 3.1 – 3.5 | 4 (4) | 2 (2) | | | |
| Age (days) | < 1 | 20 ( 21) | 18 (18.7) | 1.016 | 0.820 – 1.258 | 0.623 |
| | 1 – 3 | 34 (35.5) | 38 (39.6) | | | |
| | 4 – 7 | 22 (23) | 19 (19.8) | | | |
| | 8 – 14 | 10 (10.4) | 12 (12.5) | | | |
| | 15 – 21 | 5 (5) | 4 (4) | | | |
| | 22 – 28 | 5 (5) | 5 (5) | | | |

and percentages. Association of each variable to hyperglycemia was assessed by using logistic regression and calculations have been done for adjusted odds ratio, 95% confidence interval and *p*-value. Chi-square test was applied to find significant association and *p*-value ≤0.05 was taken as significant.

## RESULTS

The data of total 199 babies were collected and 7 were excluded due to incomplete data. Remainder 192 babies, with 96 each in 'study' and 'control' groups, were included in the study. The demographic data of study and control group were comparable in terms of gender (*p*=0.761), weight (*p*=0.256) and age (*p*=0.623) (table-I).

The study group has 1.8 times more males as compared to females (64.5% vs 35.5%). In study group, 84.4% (n=81) babies were ≤2.5kg whereas 15.6% were of 2.6–3.5 kg. Among 81 neonates of ≤2.5 kg, 56.7% (n=46) were ≤1.5 kg, 24.6% (n=20) of 1.6–2.0 kg and 18.7% (n=15) of 2.0–2.5 kg.

Seventy nine percent (n=76) babies of study group presented at age ≤7 days while 21% (n=20) between 8–28 days of life. Among 76 babies who presented during first week, 41 (54%) had hyperglycemia at age 1–3 days (fig-1).

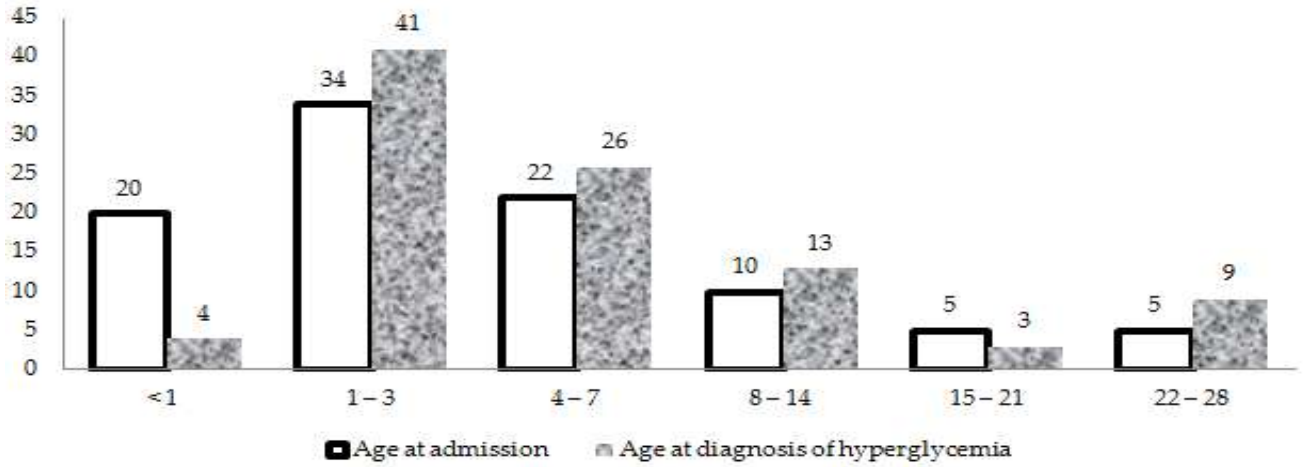


**Figure-1: Age of study group at presentation and at diagnosis of hyperglycemia.**

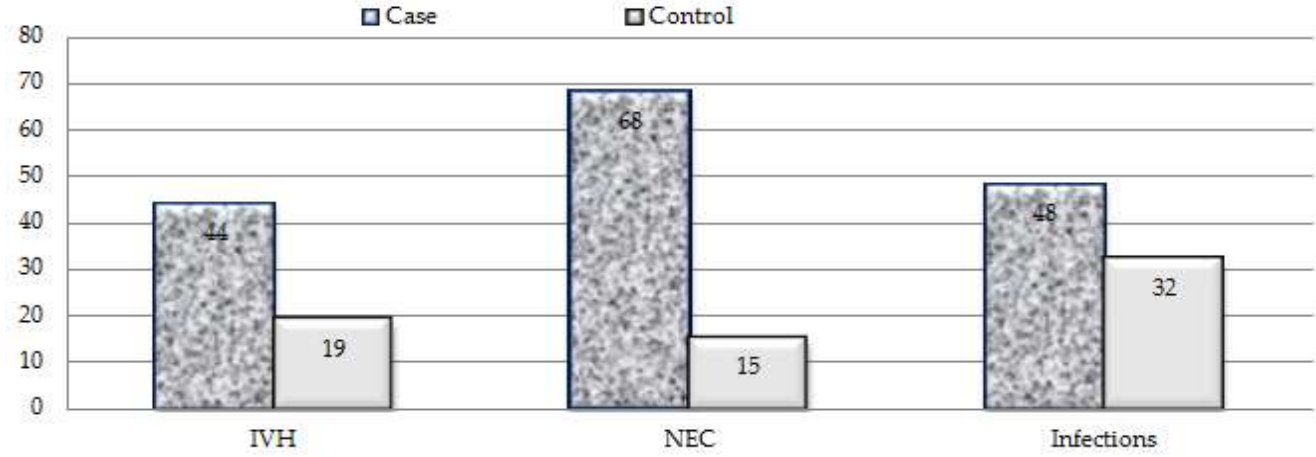


**Figure-2: Morbidity comparison.**

The number of babies that developed complications in the study group was found to be significantly high (OR 3.2263, 95% CI 0.686 to 0.854, *p*<0.001). These complications included IVH (OR 3.429, 95% CI 1.803 to 6.522, *p*<0.001),

NEC (OR 2.224, 95% CI 1.099 to 4.501, *p*=0.024) and infections (OR 2.000, 95% CI 1.116 to 3.584, *p*=0.019) (fig-2).

As regards outcome, the neonates in the study group had significantly prolonged hospital stay (OR 0.821, 95% CI 0.721 to 0.935, *p*=0.028), lower discharge rate (OR 0.739, 95% 0553 to 0.988, *p*=0.040) and higher mortality (OR 1.353, 95% CI 1.012 to 1.809, *p*=0.040) (fig-3).

## DISCUSSION

Many risk factors of neonatal morbidity and mortality have been studied but still many more are under research. Among these factors, neonatal hyperglycemia is a commonly encountered metabolic abnormality in sick neonates that has been considered to have variable relationship with morbidity and outcome of disease[9,13].

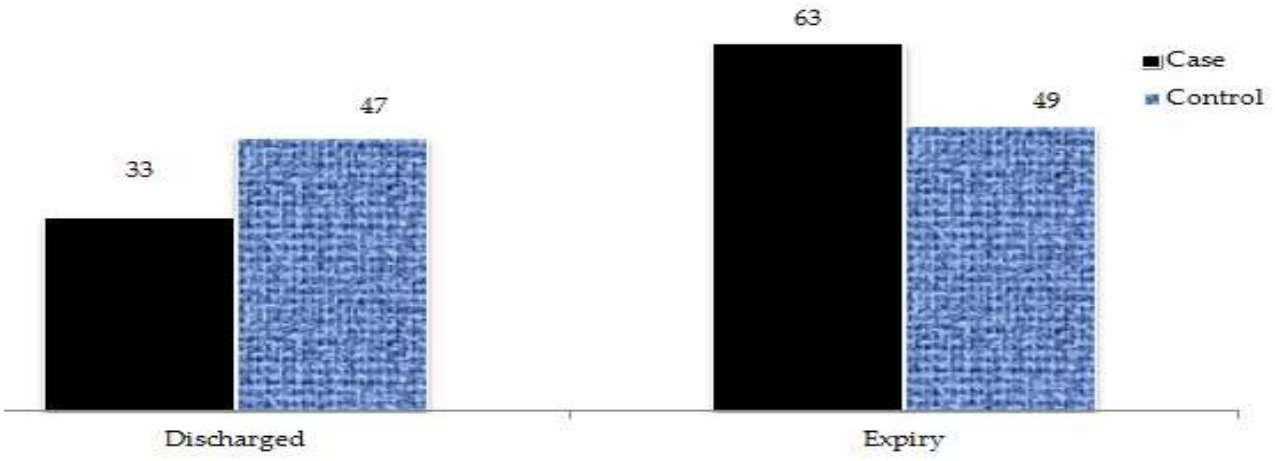


**Figure-3: Outcome comparison.**

It is a universal phenomenon that male babies are cared more and brought to hospital for medical attention[14-16]. Alexandrou and Sabzehei have found more male neonates with hyperglycemia in their study population of preterm and low birth weight babies[5,9]. Similarly in our study, hyperglycemic males were 1.8 times more as compared to female neonates.

Neonatal hyperglycemia has been shown to have indirect relationship with birth weight[17]. Rozance and Hay have commented that neonatal hyperglycemia is 18 times more common in babies of ≤ 1 kg than 1.1–2.0 kg[3]. Lower the birth weight of newborns, more are the chances to develop hyperglycemia because of intricate complex mechanism that includes increased endogenous glucose production, hypoinsulinemia, insulin receptor insensitivity or resistance, catecholamine and other similar anti-insulin hormones[1,3,18,19]. Yoo et al conducted a study on extremely low birth weight (ELBW) babies and found that 85% of babies had hyperglycemia[20]. Similarly, in a study of very low birth weight (VLBW) babies, Beardsall found hyperglycemia in 80% of newborns[21]. In our 'study group' 84.4% hyperglycemic babies were low birth weight (LBW). Although, Yoo and Beardsall included only ELBW and VLBW babies and we included hyperglycemic newborns of all birth weights, yet LBW babies constituted 84% of our study group, hence results are comparable.

During early neonatal period, especially the very first week of life, neonates are more vulnerable to have hyperglycemia. This is because of stress leading to altered glucose metabolism, resulting in hyperglycemia[22]. According to various studies, prevalence of hyperglycemia has been documented in 60-85% neonates in first seven days of life[1,5,9,14]. Similarly, according to our study, during first week of life 74% neonates were diagnosed to have hyperglycemia. In a study by Lugt et al, the mean age at the time of diagnosis of neonatal

hyperglycemia was 3.2 ± 3.7 days of life[23]. The results are comparable to our study as 58% neonates of study group had hyperglycemia at age 1-3 days.

NEC has been variably reported complication of neonatal hyperglycemia . By using Modified Bell's criteria stage II & III for diagnosis of NEC, the reported prevelance is 2% by van der Lugt et al[23], 2.9–4.1% by Mohamed et al[24] and 33% by Sabzehei[5]. In contrary to these studies, 70.83% neonates in our study group developed NEC ($p$=0.024). This high prevalence of NEC in our study group is because of difference in diagnostic criteria, as unlike other studies we had included stage I along with II and III of Modified Bell's criteria for diagnosis.

Hyperglycemia has been documented to affect white blood cells (WBC) functions hence higher chances of infections. Bekhof reported prevalence of infections in 47.2% hyperglycemic neonates[25]. In our study population 50% of hyperglycemic babies ($p$=0.019) had been found to have infection. These results are comparable because of same study design adopted by both studies. On the contrary, only 29% to 36.36% hyperglycemic babies were reported to develop infections as studied by Beardsall and Sabzehei respectively[5,21]. The low prevalence of infection in these two studies as compared to ours was because of difference in diagnostic criteria, as we have used clinical and laboratory investigations as compared to blood culture alone by others.

Hyperglycemia causes hyperosmolarity (each 18 mg/dl rise in glucose rises osmolarity by 1.0 mosm/L) and hence responsible for brain cell dehydration, capillary dilatation and cerebral bleeding[3]. Intraventricular hemorrhage in hyperglycemic neonates has been reported as 36% by Beardsall and 42% by Alexandearou[12,21]. Similarly in our study 45.83% ($p$<0.001) hyperglycemic neonates developed IVH. The comparable results of our study to other studies are because all studies had used USG cranial as diagnostic tool for IVH. On contrary, only 9% hyperglycemic neonates developed IVH as reported by Lugt et al[23]. However his study was conducted as a retrospective follow-up study in which short and long term outcome of neonatal hyperglycemia in very preterm surviving infants was studied.

Hyperglycemic neonates have been shown to have increased complications secondary to hyperglycemia, hence require prolonged hospital stay for management of these complications. Sabzehei in his study of VLBW babies found that hyperglycemic neonates had prolonged hospital stay as compared to non-hyperglycemic neonates ($p$=<0.001)[5]. Similarly, in our study, significantly prolonged hospital stay ($p$=0.028) was observed in hyperglycemic neonates as compared to control group.

Hyperglycemic neonates had increased risk of morbidity due to multiple comorbid conditions and complications. Banik and Sabzehei have shown in their studies that hyperglycemic neonates have significantly higher mortality ($p$=<0.001 and $p$=<0.002 respectively)[5,13]. Our study had shown that hyperglycemic neonates had significantly high mortality ($p$=0.04) as compare to euglycemic babies of control group.

## CONCLUSION

Hyperglycemic newborns have been shown to have not only increased risk of developing IVH, NEC and infections but also, these babies require a prolonged hospital stay and have higher risk of mortality.

## CONFLICT OF INTEREST

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

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