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Research Article

# Glycemic status and its effect in Neonatal Sepsis - A prospective study in a Tertiary Care Hospital in Nepal

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## Abstract

**Introduction:** Sepsis is an important cause of morbidity and mortality among neonates. Neonatal sepsis can alter the glucose level and both hypoglycemia and hyperglycemia may occur. A high or low blood glucose level may have a significant effect on the outcomes in patients of neonatal sepsis.

**Aims:** The aim of the study to see the glycaemic status and its effect on outcome of neonatal sepsis.

**Material and Methods:** This hospital based prospective observational cross-sectional study was conducted in Neonatal Intensive Care Unit in Universal College of Medical Sciences, a tertiary care hospital over a period of 4 months, from May 2019 to August 2019. A total of 220 Neonates suspected sepsis under the age of 28 days admitted in NICU, were studied and included in our study. Clinically suspected neonatal sepsis cases were enrolled in the study. Venous blood was collected before giving any intravenous fluid, dextrose or antibiotics and blood sugar, complete blood counts, CRP levels and blood culture were send to laboratory within half hour of collection. All patients included in this study were treated accordingly and followed up strictly. Blood glucose level and mortality of neonates having hypoglycemia, hyperglycemia were analyzed among CRP and culture positive patients. Quantitative data were expressed as mean and standard deviation. Qualitative data were expressed as frequency and percentage and comparison carried by Chi-square ($\chi 2$) test.

**Results:** A total of 220 patients clinically diagnosed as neonatal sepsis were studied. 118 (53.6%) patients were found CRP positive and 56 (25.5%) patients were blood culture positive. Glycaemic status was analyzed among CRP and culture positive patients. Majority (55.9%) patients were found normoglycemic, 35.5% were found hypoglycemic and 8.6% were found hyperglycaemic in this study. 182 (82.73%) patients were cured and 38 (17.27%) died. Mortality was high in hypoglycaemic patients (34.4%) compared with normoglycaemic patients (9.82%), but the difference was not statistically significant ($p > 0.05$) between two groups, the mortality was high in hyperglycaemic patients (58.33%) compared with normoglycaemic patients (9.82%) and the difference was statistically significant ($p < 0.05$) between two groups.

**Conclusion:** Alteration of glycaemic status occurred in septic newborn. Mortality is higher among the septic newborn with hyperglycemia. The present study found that majority of neonate with sepsis had high mortality rate when blood glucose level were either more than 145 mg/dl or less than 45 mg/dl. This signifies the importance of meticulous blood glucose estimation in cases of neonatal sepsis to improve mortality outcome.

## More Information

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**Keywords:** Glycemic status; Neonatal sepsis; Outcome; Antibiotic



## Introduction

Sepsis remains a leading cause of mortality and morbidity, especially during the first five days of life especially in low and middle-income countries (LMIC) [1]. Neonatal sepsis is defined as a clinical syndrome of bacteraemia with systemic signs and symptoms of infection in the first 4weeks of life. It encompasses various systemic infections of the newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infections. Sepsis is the commonest cause of neonatal mortality. It is responsible for about 30-50% of the total neonatal deaths in developing countries [2].

Neonatal mortality rate of Nepal is 33 per 1,000 live births and sepsis is one of the leading cause. In year B.S. 2070/71, of the total neonates presenting to government health facilities, 13.9% had possible bacterial infection and 42.1% had local bacterial infection. The major causes of neonatal deaths in Nepal are infection, birth asphyxia, preterm birth, and hypothermia [3]. Neonatal sepsis can affect blood glucose level. A neonate having sepsis develops reluctance to take feed and this can lead to hypoglycaemia. Similarly increased metabolic demand and hypothermia caused by sepsis can bring down the glucose level. Sepsis has been known to be the cause of 9.6% cases of neonatal hypoglycaemia. Increase in the production of stress hormones like adrenaline, cortisol and glucagon, in neonatal sepsis, can lead to high glucose level. Sepsis is a common cause of critical illness and hyperglycemia in the pediatric age group. Glucose is a critical nutrient for the brain. A high or low blood glucose level may have a significant effect on the outcomes in patients of culture proven and probable neonatal sepsis [4].

Despite advances in maternal and neonatal care, infection remains a frequent and important cause of neonatal and infant mortality and morbidity [5]. Neonatal mortality is associated with about 41% of all death among under-five children [6]. Glucose is a very important substrate of metabolism especially in the brain [7]. The operational threshold for hypoglycemia is defined as "that concentration of plasma or whole blood glucose at which clinicians should consider intervention, based on the evidence currently available in literature. This threshold is currently believed to be a blood glucose value of less than 40 mg/dL (plasma glucose less than 45 mg/dL) [8]. Many different neonatal groups are at a risk of developing low blood glucose concentration for example pre-term baby, large for gestational age, infant of diabetic mother, intrauterine growth restriction (IUGR), sepsis, shock, asphyxia, hypothermia, respiratory distress syndrome (RDS) [9]. Sepsis has been known to be the cause of 9.6% cases of neonatal hypoglycemia [10]. A neonate having sepsis develops reluctance to feed and this can lead to hypoglycemia. Similarly increased metabolic demand and hypothermia caused by sepsis can bring down the glucose level [11]. Severe and prolonged neonatal hypoglycemia is associated with a risk of long term neurodevelopmental sequlae like microcephaly, epilepsy, visual impairment and long-term disability. Persistent hypoglycemia leads to irreversible cellular dysfunction, organ failure and eventually death.

Hyperglycemia is defined as a plasma glucose level more than 145 mg/dl [9]. Neonatal hyperglycemia can occur in conditions like - parenteral glucose, very low birth baby, lipid infusion, sepsis, mechanical ventilation, hypoxia, surgical procedures, neonatal diabetes etc. Major clinical problem associated with hyperglycemia are hyperosmolarity and osmotic diuresis that leads to alteration of cerebral auto regulation. Hyperosmolar state can also cause water to move from intracellular compartment to extracellular compartment. The resultant contraction of intracellular volume of the brain may cause intracranial haemorrhage [9].

In neonatal sepsis, several neuroendocrine and inflammatory mediators are released which causes hyperglycemia. In septicaemia there is an increased production of stress hormone like glucagon, growth hormone, catecholamines, and glucocorticoids. These hormonal changes (also known as the counter regulatory response) and an increase in pro-inflammatory cytokines, i.e. - interleukin (IL-1, IL-6), and tumor necrosis factor (TNF) - alpha, are important factors leading to hyperglycemia [12].

A high or low blood glucose level may have a significant effect on the outcomes in patients of neonatal sepsis. A recent study in Pakistan found that those patients of neonatal sepsis with altered glucose level had higher mortality [11]. The present study was designed to determine the glycaemic status among patients with neonatal sepsis and to evaluate their association with the mortality.

## Materials and Methods

This hospital based prospective observational cross-sectional study was conducted in Neonatal Intensive Care Unit in Universal College of Medical Sciences, a tertiary care hospital over a period of 4 months, from May 2019 to August 2019. A detailed history and thorough physical examination was done in each patient on admission. Inclusion criteria were all newborn admitted to UCMS-TH NICU with screening positive sepsis or clinically suspected sepsis and neonates presence of 2 or more risk factor positive were considered as suspected sepsis were included. Patients with infants of diabetic mother and congenital anomalies were excluded. Those cases who received intravenous glucose or antibiotics before admission were also excluded from this study. Blood glucose level and mortality of neonates having hypoglycemia and hyperglycemia were analyzed. Venous blood was collected before giving any intravenous fluid, dextrose or antibiotics and blood sugar, complete blood counts, CRP levels and blood culture were send to laboratory within half hour of collection. Lumbar puncture was done in those patients who showed signs and symptoms of meningitis to obtain cerebrospinal fluid for microscopic examination, protein, glucose levels and culture. CRP levels > 6 mg/L considered as positive and less than 6 mg/L considered as negative. For this study glucose levels were divided into three groups i.e. < 45 mg/dl, 45-145 mg/dl, and > 145 mg/dl. All patients included in this study were treated accordingly and followed up strictly. The outcome and relevant data from history, physical examination and investigations were recorded in predesigned questionnaire. A total of 220 neonates suspected sepsis under the age of 28 days admitted in NICU, were studied and included in our study.

**sepsis screening criteria**

- Absolute Neutrophil Count (ANC): < 1800/cu mm
- Immature to Total Neutrophil (I/T) Ratio: > 0.2 (immature neutrophils/ANC), highly sensitive of NNS

- Total Leukocyte Count (TLC): < 5000/cu mm or > 20,000/cu mm
- CRP: > 6 mg/dL
- Micro ESR (μ-ESR): > 15 mm/1st hr, specific but moderate sensitivity
- Platelets < 150000 cu mm

### Blood culture and sensitivity

All new borns with suspect sepsis and screen positive sepsis were subjected to blood culture, 2-3 ml blood was collected with strict aseptic precaution and collected in culture vials and sent to microbiology laboratory as per the hospital protocol.

### Ethical clearance

The approval of Institutional Review Committee of Universal College of Medical Sciences, Bhairahawa, Nepal was taken before the initiation of experiment. Registration No. UCMS/IRC/116/19. All the protocols and experiments were conducted in compliance with the ethical principles and guidelines.

### Statistical analysis

Data were processed manually and analyzed with the help of SPSS (Statistical package for social sciences) Version 16.0. Quantitative data were expressed as mean and standard deviation. Qualitative data were expressed as frequency and percentage and comparison carried by Chi-square ($\chi 2$) test. A probability ($p$) value of < 0.05 was considered statistically significant and $p < 0.01$ was considered highly significant but $p > 0.05$ taken as non-significant.

## Results

A total of 220 neonates with clinical sepsis were included for the study and were evaluated accordingly.

During the study period, a total 220newborn with clinical sepsis were admitted. There were 141 (64.1%) Hindu, 55 (25.0%) Muslim, and others were 24 (10.9%). 157 (71.4%) male and 63 (28.6%) female neonate with male to female ratio of 2.5:1. However 116 (52.7%) were delivered by normal vaginal delivery and 104 (47.3%) were delivered by lower segment caesarean section. Maternal risk factor for sepsis were 66 (30.0%) and without risk factor for sepsis 154 (70.0%). PV leakage were present in 26 (11.8%) cases. 41 (18.6%) neonate were born low birth weight and 179 (81.4%) were normal weight (> 2.5 kg). 41 (18.6%) were preterm, 171 (77.7%) were term baby and 8 (3.6%) cases were post-term baby (Table 1).

The distribution of blood culture of total patient n = 220 the result showed that the number of 56 (25.5%) of patient were blood culture positive, 30 (53.4%) were normoglycemic, 22 (39.28%) were hypoglycemic and 4 (7.14%) were hyperglycaemic. In the same patient population we identified the glycaemic status but the screening of population according to the CRP positive n = 118, Majority (51.7%) of CRP positive patients were found normoglycemic, 33.9% were found hypoglycemic and only 14.4% were found hyperglycaemic.

Mortality was high in hypoglycaemic patient (34.48%) in comparison with normoglycaemic patient (9.82%) and the difference was not statistically significant ($p > 0.05$) between two groups. Mortality was also high in hyperglycaemic patient (58.33%) in comparison with normoglycaemic patient (9.82%) and the difference was statistically significant ($p < 0.05$) between two groups (Table 2).

Table 3 shows regression analysis for various risk factors for hypoglycemic babies. On multivariate logistic regression

**Table 1:** Demographic data of neonatal sepsis: (n = 220).

| S.N. | Category | Distribution | Frequency | Percentage |
|---|---|---|---|---|
| 1 | Religion | Hindu<br>Muslim<br>Others | 141<br>55<br>24 | 64.1%<br>25.0%<br>10.9% |
| 2 | Sex | Male<br>Female | 157<br>63 | 71.4%<br>28.6% |
| 3 | Mode of delivery | NVD<br>LSCS | 116<br>104 | 52.7%<br>47.3% |
| 4 | Maternal risk factor for sepsis | Yes<br>No | 66<br>154 | 30.0%<br>70.0% |
| 5 | PV leakage >18hours | Yes<br>No | 26<br>194 | 11.8%<br>88.2% |
| 6 | Maturity of baby | Pre-term<br>Term<br>Post-term | 41<br>171<br>8 | 18.6%<br>77.7%<br>3.6% |
| 7 | Weight for Age | SGA<br>AGA<br>LGA | 34<br>183<br>3 | 15.5%<br>83.2%<br>1.4% |
| 8 | Low birth weight | YES<br>NO | 41<br>179 | 18.6%<br>81.4% |

**Table 2:** Association of hypoglycemia and hyperglycemia with mortality.

| Glycemic status | Total Number (N) | Mortality n % | | p - value |
|---|---|---|---|---|
| Normoglycemia | 112 | 11 | 9.82 | 0.095$^{ns}$ |
| Hypoglycemia | 58 | 20 | 34.48 | |
| Normoglycemic | 112 | 11 | 9.98 | 0.044 |
| Hyperglycaemic | 12 | 7 | 58.33 | |

**Table 3:** Risk factors for hypoglycemic babies (Multivariate regression analysis)

| Risk factors | Odds Ratios (95% confidence interval) | p - value |
|---|---|---|
| Sex of children | | 0.42 |
| Female | 1 | |
| Male | 1.56 [0.73-3.45] | |
| Gestational Week | | 0.003 |
| Less or equal to 30 | 5.6 [1.23-13.84] | |
| > 30 | 1 | |
| Low Birth weight | | < 0.001 |
| No | 1 | |
| Yes | 2.23 [0.52-6.49] | |
| Maternal risk for sepsis | | 0.02 |
| No | 1 | |
| Yes | 4.63 [1.89-9.87] | |
| WBC | | 0.007 |
| (5000-20000/cm) | 1 | |
| < 5000 | 1.85 [0.48-5.93] | |
| > 20000 | 2.16 [0.76-8.44] | |

gestational weeks ≤ 30 weeks (OR 5.6; CI 0.73-3.45) and maternal risk factors for sepsis (OR 4.63; CI 1.89-9.87) were independent predictors for hypoglycemia in babies admitted to NICU. Sex of the baby (OR 1.56; CI 0.73-3.45), low birth weight (OR 2.23; CI 0.52-6.49), and total leukocyte count more than 18000 cells/mm3 (OR 2.16; CI 0.76-8.44) did not show any significant association for hypoglycemia in babies admitted to NICU.

Table 4 shows regression analysis for various risk factors for hypoglycemic babies. On multivariate logistic regression analysis babies born to maternal risk factors for sepsis had 6-fold increased risk for hyperglycemia compared to babies without any maternal risk factors (OR 6.63; CI 1.67-11.43, $p < 0.001$). Babies with gestational age ≤ 30 weeks had about 8 times less chance of having hyperglycemia compared to > 30 weeks babies (OR 7.87; CI 0.63-34-23, $p = 0.02$).

## Discussion

This observational study was carried out with an aim to determine the glycaemic status in neonatal sepsis and to evaluate the association of hypoglycemia and hyperglycemia with mortality in patient of neonatal sepsis.

In this study it was observed that majority (51.7%) of the patients were normoglycemic (45-145 mg/dl) followed by 33.9% hypoglycemic (< 45 mg/dl) and 14.4% hyperglycaemic (> 145 mg/dl). Ahmad and Khalid, [7] study showed the glucose levels were below 40 mg/dl in 9.9%, between 40 mg/dl to 100 mg/dl in 64.1%, between 101 mg/dl to 200 mg/dl in 18.9% and above 200 mg/dl in 6.9% patients. In another study Begum, et al. observed hyperglycemia in 4.62% of their study patients [13]. A neonate having sepsis develops reluctance to take feed and this can lead to hypoglycemia. Similarly increased metabolic demand and hypothermia caused by sepsis can bring down the glucose level.

During the past few years many studies have been conducted to ascertain importance and consequences of hyperglycemia and hypoglycemia in both paediatric and adult patients. Several studies have shown that hyperglycemia is associated with adverse outcomes in the paediatric age group. Different reasons for this association have been proposed e.g. enhanced apoptosis, increased production of cytokine, hyper coagulation, acute dyslipidaemia, endothelial dysfunction etc. A study by Wintergerst, et al. has shown that hyperglycemia, hypoglycemia and glucose variability were associated with increased mortality rates and increased length of stay in PICU [14].

**Table 4:** Risk Factors for hyperglycaemic babies [multivariate regression analysis].

| Sex of children | Odds ratio | *p* - value |
|---|---|---|
| Female | 1 | |
| Male | 2.45 [1.28-6.21] | 0.65 |
| Gestational week | | |
| Less or equal to 30 | 7.87 [0.63-34.23] | |
| > 30 | 1 | 0.02 |
| Low birth weight | | |
| No | 1 | |
| Yes | 3.45 [0.59-8.42] | 0.004 |
| Maternal risk for sepsis | | |
| No | 1 | |
| Yes | 6.63 [1.67-11.43] | < 0.001 |
| WBC count | | |
| [5000- 20000] /cm | 1 | |
| < 5000 | 2.34 [0.87-7.29] | |
| > 20000 | 3.89 [0.33-14.43] | 0.009 |

In this present study It was observed that mortality was high in hypoglycaemic patient (34.48%) compared with normoglycaemic patient (9.82%), but the difference was not statistically significant ($p > 0.05$). Ahmad and Khalid11 found 32% mortality in hypoglycemic patient which was consistent with the finding of present study.

It was also observed in this current study that mortality was so high in hyperglycemic patient (58.33%) compared with normoglycaemic patient (9.82%), which was statistically significant ($p < 0.05$). Lugt, et al. found that 27 out of 66 infants with hyperglycemia (41.0%) died [15]. Similar finding also observed by Ahmad & Khalid which are comparable with the present study. Patients of neonatal sepsis with high blood glucose levels were at increased risk of death, and should be treated as high risk patients [7]. Patients of neonatal sepsis should be detected early and should receive early treatment, before hyperglycemia set in. Kao, et al. Who found severe hyperglycemia was associated with increased death and sepsis in ELBW infants [16]. Recurrent hypoglycemia in a neonate and start treatment as soon as possible, in order to prevent brain damage. Low blood glucose may also be a warning sign as part of more complex disorders. Clinical and additional laboratory findings can indicate the possible etiology of hypoglycemia, enabling cause targeted management. When hypoglycemia is controlled and normoglycaemic is achieved with regular meals or appropriate therapy, the neonate may be discharged home. Follow-up of neonates who have had persistent or recurrent hypoglycemia is warranted to watch for changed since, low blood glucose is physiological a few hours after birth, and the main goal is to recognize persistent or metabolic and endocrine pathways.

In a study done by Tam, et al. found neonatal hypoglycemia was associated with additional risks in the setting of neonatal encephalopathy with increased corticospinal tract injury and adverse motor and cognitive outcomes [17]. In a study done by sekitoleko, et al. found that hypoglycemia was an independent risk factor for in hospital mortality in patients with severe sepsis [18]. In a study done by Stomnaroska, et al. found neonatal hypoglycemia was a significant factor in the overall neonatal mortality and infections, But Spearman tests showed weak direct correlation, without statistical significance [19]. Similar findings was found on a Study done by Islam, et al. [20], showing that mortality was higher among the septic newborn with hyperglycemia (50%) compared

to normoglycaemic patient (10.8%) and the difference was statistically significant ($p < 0.05$) between two groups [20]. Yadav, et al. found the incidence of culture positive sepsis was 6.5% of the total cases of suspected sepsis, which was much lower than the present study [21].

Patients of neonatal sepsis and probable sepsis, with high glucose levels or with hypoglycemia, are at increased risk of death, and should be treated as high risk patients. Patients of neonatal sepsis and probable sepsis, should be detected early and should receive early treatment, before hyperglycemia and hypoglycemia set in. Studies are needed to ascertain whether or not more stringent control of glucose levels in patients of neonatal sepsis can improve outcomes.

## Conclusion

Alteration of glycemic status occurred in septic newborn. Our study showed mortality is higher among the septic newborn with hyperglycemia. The incidence of hypoglycemia was high as compared to hyperglycemia. Neonatal hypoglycemia and hyperglycemia was a significant factor in the overall mortality in neonatal sepsis.

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