Original Article

Glycemic Status and its effect on outcome of neonatal sepsis in a tertiary care hospital in Nepal

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ABSTRACT

BACKGROUND

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life. Neonatal sepsis is one of the leading causes of hospital admissions and neonatal deaths. Glucose remains the major source of energy for neonates and neonate's brain is largely dependent upon glucose. Altered blood glucose level is common in neonatal sepsis. Both high and low blood glucose level is found to have significant negative impact on outcome of neonatal sepsis and is associated with high mortality. Altered blood glucose level is common in neonatal sepsis.

AIMS

This study aimed to determine the effect of glycemic status on outcome of neonatal sepsis in terms of mortality and duration of hospital stay

METHODS

A prospective observational study was performed over a period of one year in 91 neonates admitted with diagnosis of neonatal sepsis in Neonatal Intermediate Care Unit (NIMCU) and Neonatal Intensive Care Unit (NICU) of Kanti Children's Hospital who fulfilled the inclusion criteria. Random blood glucose was sent along with other investigations while performing septic screening before infusing intravenous fluids or other medications. These neonates were followed in NIMCU or NICU and immediate outcome and duration of hospital admission were recorded. Statistical analysis was done using SPSS 23.

RESULTS

Of total 91 neonates included in the study, altered glycemic status was present in 15% cases with hypoglycemia in 12% cases and hyperglycemia in 3% cases. Mortality among hypoglycemic neonates was high (9%) in comparison to normoglycemic neonates (4%) but the difference in mortality among these two groups was not statistically significant (p-value=0.44). Mortality among hyperglycemic neonates was significantly high (33%) in comparison to normoglycemic neonates (4%), which is statistically significant (p value=0.02). The median length of hospital admission among normoglycemic, hypoglycemic and hyperglycemic neonates was 7(3-21) days, 5(4-22) days and 5(5-9) days respectively, which is not statistically significant (p value=0.74)

CONCLUSIONS

Altered glycemic status is common in neonatal sepsis. Mortality is significantly high in septic neonates with hyperglycemia.

KEYWORDS

neonatal sepsis, glycemic status, blood culture, outcome

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INTRODUCTION

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life.1 It encompasses various systemic infections of newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infections.2 According to WHO estimates, every year over 4 million babies die in the first four weeks of life and neonatal sepsis remains one of the major cause of neonatal deaths.3

Neonatal sepsis is one of the leading causes of hospital admissions in Nepal and also one of the leading cause of neonatal death.4 As per Nepal Demographic Health Survey 2016, the neonatal mortality rate of Nepal is 21/1000 live births which accounts for 66% of IMR (32/1000 live births).5 Neonatal sepsis may be divided into two types depending upon whether the symptoms appear within ≤72 hours of life (EONS) or ≥72hours of (LONS)6, 7. Early onset infections are usually caused by organisms colonized in the maternal genital tract or in the delivery area.6 Early onset sepsis manifests frequently as pneumonia and less commonly as septicemia or meningitis. Late onset sepsis is usually caused by the organisms thriving in the external environment of the home or the hospital. The onset of symptoms is beyond 72 hours of life and the presentation is that of septicemia, pneumonia or meningitis7..

Glucose remains the major source of energy for neonates and neonate's brain is largely dependent upon glucose8. At birth, the neonate switches from having a continuous supply of glucose from the mother through the placenta to maintaining its own glucose supply during the intermittent feeds9. Glucose homeostasis requires a balance between utilization and production from the liver. This balance is controlled by insulin and counter regulatory hormones namely glucagon, growth hormone, cortisol and catecholamines.9

Hypoglycemia is associated with adverse outcome in neonates. 10, 11There is no exact consensus in literature on exact definition of hypoglycemia however, target blood glucose for asymptomatic neonate is more than 40 mg/dl for infants below 4 hours of life and more than 45 mg/dl for neonates above 4 hours of life.12 Neonatal sepsis is important cause of hypoglycemia in neonates accounting for 9.6% cases in one study.8 Factors responsible for hypoglycemia in neonatal sepsis are decreased feeding, increased metabolic demand and hypothermia.13, 14 Prolonged and severe hypoglycemia in neonates leads to long term neurodevelopmental sequelae such as microcephaly, epilepsy, visual impairment and long term disability. Persistent hypoglycemia can lead to irreversible cellular dysfunction, organ failure and eventually death.14

Hyperglycemia is defined as whole blood glucose level more than 125 mg/dl or plasma glucose level more than 145 mg/dl.15 Hyperglycemia is associated with hyperosmolarity and osmotic diuresis which can lead to alteration of cerebral autoregulation resulting in intracranial hemorrhage or no symptom at all.13, 14 Several neuroendocrine hormones and inflammatory mediators are released in neonatal sepsis, responsible for hyperglycemia. Stress hormones like glucagon, growth hormones (GH), catecholamines, glucocorticoids, pro-inflammatory cytokines i.e. interleukins (IL-1, IL-6) and tissue necrosis factors (TNF-α) are produced in neonatal sepsis leading to hyperglycemia.14, 16. Both high and low blood glucose level has significant effect on outcome of neonatal sepsis and is associated with high mortality.13, 14

Altered blood glucose level is common in neonatal sepsis and has significant effect on outcome of neonatal sepsis and is associated with high mortality. There are limited studies on blood glucose level in neonatal sepsis in Nepal. Hence this study is planned to study the glycemic status and its effect on outcome of neonatal sepsis in terms of mortality and duration of hospital stay.

METHODS

1. Study Design and participants

This study was a prospective observational study, carried out in Neonatal Intermediate Care Unit (NIMCU)/Neonatal Intensive Care Unit (NICU), Kanti Children's Hospital (KCH), Maharajgunj, Kathmandu, Nepal from 19th January 2018 to 18th January 2019.

All neonates admitted in NIMCU/NICU meeting inclusion criteria were enrolled into the study.

Inclusion Criteria:

term neonates admitted with provisional diagnosis of neonatal sepsis with birth weight of ≥2500 gm and ≤4000 gm

Exclusion criteria:

- infants of diabetic mother
- infants with perinatal asphyxia
- infants with meconium aspiration syndrome
- infants with gross congenital anomalies
- infants who received intravenous glucose or antibiotics before admission

-infants who leave against medical advice

Sample size Calculation

Sample size was calculated using formula

N=Zα2×P(1-P)/D2, where

N= sample size

Zα= z deviate corresponding to desired reliability level (1.96) for 95% reliability

P= estimated proportion in population (28.8%)

The study showed that incidence of altered glycemic status in neonatal sepsis is 28.8%.14

Q= 100-P (if P is in %) =(100-P) =(100-P) =71.2

D= maximum tolerable error =10%

So the minimum sample size was 79 and in this study total cases enrolled were 91.

Sampling technique:

Consecutive. All neonates admitted to NIMCU/NICU of KCH with diagnosis of neonatal sepsis who fulfill the inclusion criteria during the study period.

2. Data Collection

Data was collected prospectively on neonates admitted after taking informed written consent from the parents or caretakers.

Detailed history and complete clinical examination was performed by researcher. Various laboratory investigations (CBC, RBS, RFT, Blood C/S, Urine RE, CRP, TSB and Chest X-ray, CSF examination) were performed and evaluated as per hospital protocol.

At the time of admission of neonates in NIMCU/NICU, blood was drawn by doctor, nursing staff or laboratory staff before administering any intravenous fluid or drug infusion. Blood glucose examination was carried out at Emergency laboratory of KCH (Glucose oxidase/peroxidase method) by on duty laboratory staffs and they were asked to process the blood sample within 30 minutes of sample collection.

Initial blood glucose level of study population was noted and treated as per hospital protocol.

3. Data Analysis

Data were entered, edited and coded in SPSS 23. The qualitative data of the study variables were expressed in frequency and percentages and quantitative data were summarized with the help of mean, median and standard deviation. The data were represented through bar diagrams, pie diagrams and frequency distribution tables. Association between blood glucose values and mortality was tested with the help of a Fisher Exact test. Relation between duration of stay at NIMCU/ NICU and blood glucose values was tested through ANOVA. p value of <0.05 was considered as statistically significant.

4. Ethical consideration

The study was conducted after approval from the Institutional Review Board (IRB) of NAMS (Ref no. 518). All the parents of children who were included in the study were informed about various aspect of the study and written consent was taken from mothers or fathers or caretakers.

Operational definitions:

Neonatal Forum of India has classified neonatal sepsis as probable (clinical) sepsis and culture positive sepsis17

Probable (Clinical) sepsis: In an infant having clinical picture suggestive of septicemia, if there is the presence of any one of the following criteria:

- Existence of predisposing factors: maternal fever or foul smelling liquor or prolonged rupture of membranes (> 24 hrs) or gastric polymorphs (> 5 per high power field).
- Positive septic screen: - presence of two of the four parameters namely,
  - o TLC (< 5000/mm3),
  - o Band to total polymorph nuclear cells ratio of > 0.2,
  - o Absolute neutrophil count < 1800/mm3,
  - o C-reactive protein (CRP) > 1 mg/dl and
  - o Micro ESR > 10 mm/first hour.
- Radiological evidence of pneumonia.

Culture positive sepsis: In an infant having clinical picture suggestive of septicemia, pneumonia or meningitis, if there is presence of either of the following:

- Isolation of pathogens from blood or CSF or urine or abscess.
- Pathological evidence of sepsis on autopsy.

Blood glucose will be categorized12, 15 as

- normoglycemia: 45-145 mg/dl
- hypoglycemia: <40 mg/dl (if <4 hours of life) and <45 mg/dl (if >4 hours of life)
- hyperglycemia: >145 mg/dl:

RESULTS

In the present study, a total of 92 cases were studied, out of which 1 case who left against medical advice was excluded from the study. Total of 91 cases were taken in the study and were analyzed.

1. Age Distribution

The median age of the study population was 7(1-28) days. As shown in figure 1, much higher number of neonates presented with neonatal sepsis in first week of life which constitute half of the cases as compared to neonates presenting with neonatal sepsis in second, third and fourth week of life which constitute one fifth, one tenth and one fifth cases respectively.

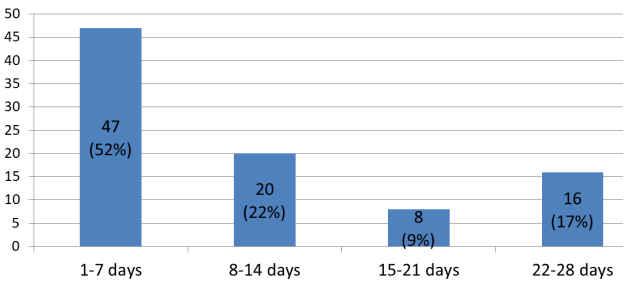

Figure 1: Age distribution (n=91)

2. Sex distribution

In the present study, males outnumbered females in the total number of study population. The male: female ratio was 1.33:1, as shown in figure 2.

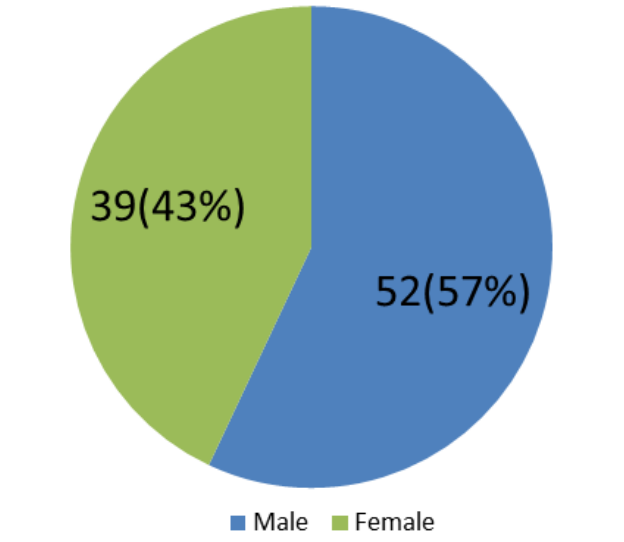

Figure 2: Sex distribution (n=91)

3. Type of Neonatal Sepsis

As shown in figure 3, most of the cases belonged to LONS which constitute three quarter of cases and EONS constitute one quarter of cases.

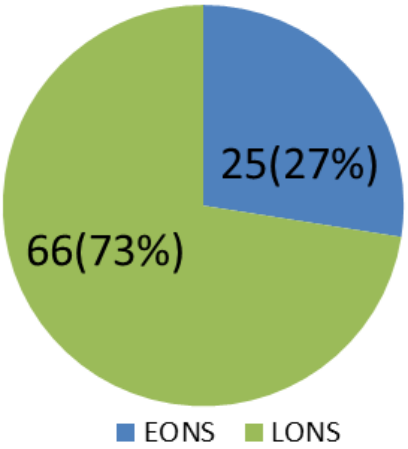

Figure 3: Types of sepsis (n=91)

4. Glycemic Status

As shown in the figure 2, significantly high number of neonates were normoglycemic (85%) as compared to hypoglycemic (12%) and hyperglycemic (3%).

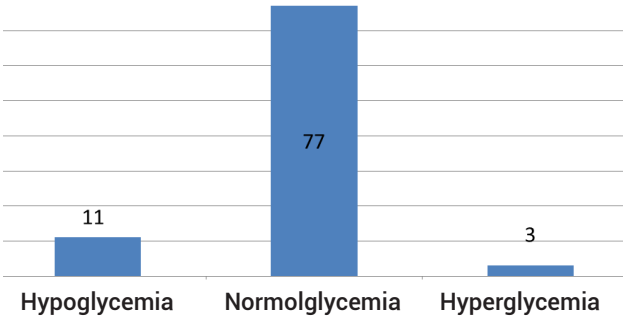

Figure 4: Glycemic status among study population (n=91)

5. Distribution by Blood Culture Status

Blood culture was postitive in 17 patients. As seen in the figure 5, Staphylococcus aureus was isolated in significantly higher number of culture positive cases (82%) as compared to other organisms such as Coagulase negative staphylococcus aureus (6%), Enterococcus fecalis (6%) and Acinetobacter sps (6%).

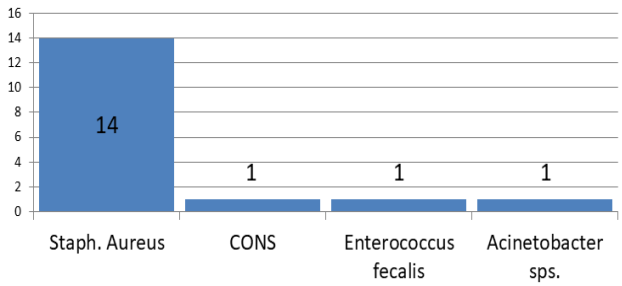

Figure 5: Organisms isolated in blood culture (n=16)

6. Chest X ray And CSF Findings

In the present study, chest x-ray was found to be normal in four fifth cases and pneumonia was found in one fifth cases. Higher number of neonates had normal CSF analysis result (70%) as compared to those having meningitis (12%) however CSF analysis was not performed in 18% cases.

7. Glycemic status in types of neonatal sepsis

In the current study, significantly higher number of neonates belonged to clinical (probable) sepsis group (76%) compared to culture positive sepsis group (24%).

As shown in table 1, among hypoglycemic neonates four fifth cases had clinical sepsis and one fifth cases had culture positive sepsis whereas among normoglycemic neonates three quarter had clinical sepsis and one quarter had culture positive sepsis group and among hyperglycemic neonates had clinical sepsis however these results are not statistically significant.

Table 1. Age distribution of study patients.

Glycemic status	Types of sepsis				Total		P value
	Clinical (Probable) sepsis		Culture positive sepsis				
	Number	Percent	Number	Percent	Number	Percent	0.52
Hypoglycemia	9	82	2	18	11	100	
Normoglycemia	57	74	20	26	77	100	
Hyperglycemia	3	100	0	0	3	100	
Total	69	76	22	24	91	100	

8. Glycemic status in relation to CRP

As shown in table 2, among hypoglycemic neonates about one third of the cases were CRP positive and about two third of the cases were CRP negative, among normoglycemic neonates one quarter of cases are CRP positive and three quarter of cases are CRP negative and among hyperglycemic neonates all neonates were CRP negative but these results were not statistically significant (p>0.05)

Table 2. Glycemic status in relation to CRP (n=91)

Glycemic status	CRP				Total		P value
	Positive		Negative		Number	Percent	
	Number	Percent	Number	Percent			
Hypoglycemia	4	36.4	7	63.6	11	100	0.39
Normoglycemia	18	23.4	59	76.6	77	100	
Hyperglycemia	0	0	3	100	3	100	
Total	22	24.2	69	75.8	91	100	

9. Outcome

In the present study, significantly high number of cases were discharged (95%) in comparison to mortality (5%), as shown in figure 6.

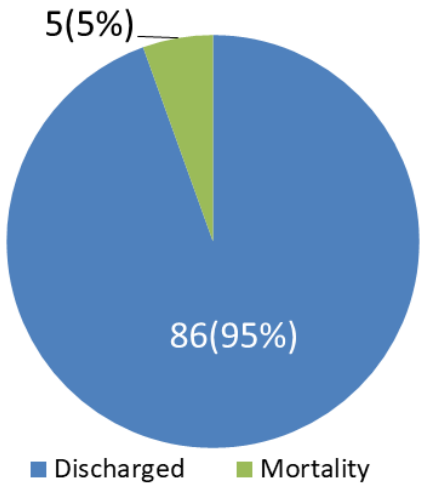

Figure 6: Outcome among study population (n=91)

10. Association of glycemic status with outcome

10.1 Association of hypoglycemia with outcome

As shown in table 3, mortality was higher in hypoglycemic neonates (9%) as compared to normoglycemic neonates (4%) but this is not statistically significant (p>0.05).

Table 3: Association of hypoglycemia with outcome

Glycemic status	Outcome				Total		P value
	Discharged		Mortality		Number	Percent	
	Number	Percent	Number	Percent			
Hypoglycemia	10	91	1	9	11	100	0.44
Normoglycemia	74	96	3	4	77	100	
Total	84	95	4	5	88	100	

10.2 Association of hyperglycemia with outcome

As shown in table 4, mortality among hyperglycemic neonates (33%) is significantly high as compared to normoglycemic neonates (4%) which is statistically significant (p<0.05).

Table 4: Association of hyperglycemia with outcome

Glycemic status	Outcome				Total		P value
	Discharged		Mortality		Number	Percent	
	Number	Percent	Number	Percent			
Hypoglycemia	74	96	3	4	77	100	0.02
Normoglycemia	2	67	1	33	3	100	
Total	76	95	4	5	80	100	

11. Length of Hospital Stay

In the present study, median length of stay among hypoglycemic neonates, normoglycemic neonates and hyperglycemic neonates were 5(4-22) days, 7(3-21) days and 5(5-9) days respectively which is not statistically significant (p>0.05).

Table 5: Length of hospital stay among study population

Glycemic status	Median duration of hospital admission in days (range)	P value
Hypoglycemia	5 (4-22)	0.742
Normoglycemia	7 (3-21)	
Hyperglycemia	5 (5-9)	

In the present study, median length of stay among hypoglycemic neonates, normoglycemic neonates and hyperglycemic neonates were 5(4-22) days, 7(3-21) days and 5(5-9)days respectively which is not statistically significant (p>0.05).

DISCUSSION

Neonatal sepsis is one of the leading causes of neonatal morbidity and mortality.18 The early diagnosis of neonatal sepsis is difficult because clinical signs, particularly early in the course of disease, are hard to distinguish from other causes of neonatal diseases.19 Blood culture has been considered as gold standard for detecting bacterial sepsis. However, blood culture is time-consuming and the distri¬bution of pathogens associated with neonatal sepsis is wide.20 Thus, for early diagnosis and treatment of the disease, it is meaningful to continue summing up and analyzing the clinical signs, pathogenic bacteria and antimicrobial resistance of neonatal sepsis. The initial diagnosis of sepsis is usually by a clinical suspicion because it is imperative to begin treatment before the results of cultures are available depending on the followings- temperature irregularity, change in the behavior, skin changes, feeding or cardiopulmonary or metabolic problems. 20

With this knowledge in mind, it is provocative that there are many articles on biomarkers for neonatal sepsis. Various studies have found that hypoglycemia and hyperglycemia both can the manifestation of neonatal sepsis and clinical features of these conditions and neonatal sepsis often overlap; it is possible that neonates with neonatal sepsis can have altered glycemic status without any specific signs and symptoms.14, 21 Altered glycemic status is associated with significant morbidity and mortality and long term neurodevelopmental sequelae such as microcephaly, epilepsy, visual impairment and long term disability. 21

Out of 91 cases, 52 (57%) were male and 39 (43%) were female. In this study, a male predominance with male to female ratio of 1.3:1 was observed, which is in line with findings from several previous studies, which have reported male to female ratio ranging from 1.2-1.8.22-24 All these studies suggest the possibility of sex linked factor in host susceptibility. This male preponderance might be due to genetic susceptibility of male patients to infection. In our part of world, it might also be due to patriarchal system of our society which gives more emphasis to the male child.

In this study, percentage of LONS and EONS was 73% (66) and 27% (25) respectively. Previous studies have reported similar findings with LONS percentage ranging from 60-90%, and EONS ranging from 15-35%.22, 25, 26 In this study, the CRP was positive in 24% cases. Previous studies have reported CRP positivity rates of 15-44 %.14, 27 The difference in results among various studies may be due to different inclusion criteria in different studies.

In this study positive blood culture accounts for 19% of total cases, comparable to other similar studies done in our part of the world such as by Gyawali N et al (14%) and Kumar P et al (11%).

Lower positive blood culture of 9% and 6% has been reported by Yadav AK et al and Naher BS et al. 27, 28 Difference in blood culture positivity rate among different studies may be due use of different quality of culture media for culture of the organisms and difference in inclusion criteria of the study population. Staphylococcus aureus was the most predominant organism to be isolated. , isolated in 82% of the blood culture positive cases, consistent with previous studies.22, 25, 26 This study showed statistically significant predominance of Staph aureus in late onset sepsis as compared to early onset sepsis.

In this study, altered blood glucose was found in 15% of the patients (hypoglycemia in 12% and hyperglycemia in 3%). Our study shows lower incidence of altered blood glucose levels compared to previous studies, such as Islam MS et al reporting 28.8 % incidence of altered blood glucose levels from their studies in Bangladesh.14 Similarly a study done in Pakistan by Bhutta et al found hyperglycemia in 21% of neonates with neonatal sepsis.29 Najatri N et al found neonatal sepsis as the cause of hypoglycemia in 7.1% of the case.8 In this study, incidence of hypoglycemia and hyperglycemia was lower than in other studies because most of cases admitted at our centre are referred cases from other centre who had already received treatment were excluded from my study and all the preterms and low birth weight neonates were excluded from my study in which the incidence of altered glucose level is quite higher than in term and appropriate for gestational age neonates.

Among blood culture positive neonates, 12% (2) were hypoglycemic, 88% (14) were normoglycemic but none were hyperglycemic. Islam MS et al found that 19% were hypoglycemic, 57.2% were normoglycemic and 23.8% were hyperglycemic among blood culture positive neonates.14

In this study, mortality among normoglycemic, hypoglycemic and hyperglycemic neonates was 4%, 9% and 33%

respectively. The mortality rate in our study is lower however our study shows ascending pattern of mortality from normoglycemia, hypoglycemia and hyperglycemia, which is comparable to finding from other studies. Similar study done in Bangladesh by Islam MS et al reported the mortality among normoglycemic, hypoglycemic and hyperglycemic neonates to be 10.8%, 42% and 50% respectively.14 In another study conducted in Pakistan by Ahmad S, mortality rate was 32%, 9.9%, 23.2% and 48.6% in neonates with blood glucose below 40 mg/dl, between 40 mg/dl and 100 mg/dl, between 101 mg/dl to 200 mg/dl and above 200 mg/dl respectively.13 Similarly, Bhutta ZA et al reported 39% the mortality among hyperglycemic neonates with neonatal sepsis.29 In a study conducted at Stanford University, Wintergerst KA et al found that mortality rate among hypoglycemic and hyperglycemic child was 16.5% and 15.2% respectively.30 This discrepancy might be because referred cases from other centre who had already received treatment were excluded from this study . In this study, the median length of stay in normoglycemic, hypoglycemic and hyperglycemic neonates was 7(3-21) days, 5(4-22) days and 5(5-9) days respectively. Hyperglycemia is found to be associated with increased length of hospital stay in childrens.30, 31 However the result of our study did not show statistically signifificant difference. It might be because in this study most of the neonates were normoglycemic and sick cases which were usually referred from other centre receiving treatment previously were excluded from this study in whom the risk of altered glycemic status is high.

LIMITATIONS

- The study may not be entirely representative of the whole neonatal population of our country since it is a hospital-based study done on a relatively small sample size of 91 cases.
- Because of the resource constraint we had difficulty in defining suspected neonatal sepsis. Addition of other markers of sepsis such as serial measurement of CRP quantitatively, procalcitonin, serum ferritin, P- and E-selectins, interleukin 2, soluble receptor α, interleukin18 neutrophil elastase etc in the diagnosis of neonatal sepsis could have helped in the accurate diagnosis of sepsis and outcome of the patient.

CONCLUSION

Altered glycemic status (hyperglycemia or hypoglycemia) in neonates is associated with poor outcome than in normoglycemic neonates. The results of this study thus underscores need of a large study on close monitoring of blood sugar levels and appropriate intervention in neonatal sepsis with altered glycemic status

REFERENCE

1. Sankar MJ, Agarwal R, Deorari AK, Paul VK. Sepsis in the newborn. The Indian Journal of Pediatrics. 2008;75:261-6.
2. Bang AT, Bang RA, Baitule SB, Reddy MH, Deshmukh MD. Effect of home-based neonatal care and management of sepsis on neonatal mortality: field trial in rural India. The lancet. 1999;354(9194):1955-61.
3. Organization WH. Neonatal and perinatal mortality: country, regional and global estimates: World Health Organization; 2006.
4. Pradhan Y, Upreti SR, Pratap KC N, KC A, Khadka N, Syed U, et al. Newborn survival in Nepal: a decade of change and future implications. Health policy and planning. 2012;27(suppl_3):iii57-iii71.
5. Nepal Demographic Health Survey 2016. Ministry of Health,Nepal, New Era, ICF; 2017, Nov.
6. Paul VK. Neonatal Sepsis. In: Paul VK, Gupta P, editor. GHAI Essential Pediatrics. 5th ed: Mehta Publisher; 2001. p. 141-3.
7. Agarwal R PV, Deodari AK. Neonatal Sepsis. In: Paul VK BA, editor. GHAI Textbook of Pediatrics. 8th ed: CBS; 2013. p. 163-5.
8. Najati N, Saboktakin L. Prevalence and underlying etiologies of neonatal hypoglycemia. Pakistan Journal of Biological Sciences. 2010;13(15):753.
9. L Sunehag A, W Haymond M. Glucose extremes in newborn infants. Clinics in perinatology. 2002;29(2):245-60.
10. Sunehag AL, Haymond MW. Glucose extremes in newborn infants. Clinics in perinatology. 2002;29(2):245-60.
11. Kairamkonda V, Khashu M. Controversies in the management of hyperglycemia in the ELBW infant. Indian Pediatrics. 2008;45(1):29.
12. Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics. 2011;127(3):575-9.
13. Ahmad S, Khalid R. Blood glucose levels in neonatal sepsis and probable sepsis and its association with mortality. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP. 2012;22(1):15-8.
14. Islam MS, Mia MAH, Akhter KR, Haque M, Malik M. Glycemic Status and its Effect in Neonatal Sepsis in a Tertiary Care Hospital. Bangladesh Journal of Child Health. 2017;40(1):21-5.
15. Wilker RE. Hypoglycemia and Hyperglycemia. In: Cloherty JP EE, Hansen AR, Stark AR, editor. Manual of Neonatal Care. 7th ed. Philadelphia: Lippincott Williams and Wilkins; 2012. p. 284-96.
16. Branco RG, Tasker RC, Garcia PCR, Piva JP, Xavier LD. Glycemic control and insulin therapy in sepsis and critical

illness. Jornal de pediatria. 2007;83(5):S128-S36.

17. Tripathi S, Mallik GK. Neonatal sepsis: past, present and future; a review article. Internet Journal of Medical Update. 2010;2(5):45-54.
18. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. The lancet. 2017;390(10104):1770-80.
19. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. Clinical microbiology reviews. 2014;27(1):21-47.
20. Shoukry LR, Mohamed AN, Sharaf AE, Osman OB. Diagnostic markers for early detection of neonatal sepsis. Journal of Scientific Research in Medical and Biological Sciences. 2021;2(3):13-26.
21. Alsaleem M, Saadeh L, Kamat D. Neonatal hypoglycemia: a review. Clinical pediatrics. 2019;58(13):1381-6.
22. Shrestha N, Subedi K, Rai G. Bacteriological profile of neonatal sepsis: a hospital based study. J Nepal Paediatr Soc. 2011;31(1):1-5.
23. Shrestha R, Rai S, Khanal L, Manda P. Bacteriological study of neonatal sepsis and antibiotic susceptibility pattern of isolates in Kathmandu, Nepal. Nepal Med Coll J. 2013;15(1):71-3.
24. Upadhyay A, Aggarwal R, Kapil A, Singh S, Paul V, Deorari A. Profile of neonatal sepsis in a tertiary care neonatal unit from India: A retrospective study. Journal of Neonatology Vol. 2006;20(1).
25. Chapagain R, Acharya R, Shrestha N, Giri R, Bagale B, Kayastha M. Bacteriological Profile of Neonatal Sepsis inNeonatal Intermediate Care Unit of Central Paediatric Referral Hospital in Nepal. 2015.
26. Shrestha P, Das B, Bhatta N, Jha D, Das B, Setia A, et al. Clinical and bacteriological profiles of blood culture positive sepsis in newborns. Journal of Nepal Paediatric Society. 2007;27(2):64-7.
27. Naher B, Mannan M, Noor K, Shahiddullah M. Role of serum procalcitonin and C-reactive protein in the diagnosis of neonatal sepsis. Bangladesh Medical Research Council Bulletin. 2011;37(2):40-6.
28. Yadav AK, Wilson C, Prasad P, Menon P. Polymerase chain reaction in rapid diagnosis of neonatal sepsis. Indian pediatrics. 2005;42(7):681.
29. Bhutta ZA, Yusuf K. Neonatal sepsis in Karachi: factors determining outcome and mortality. Journal of tropical pediatrics. 1997;43(2):65-70.
30. Wintergerst KA, Buckingham B, Gandrud L, Wong BJ, Kache S, Wilson DM. Association of Hypoglycemia, Hyperglycemia, and Glucose Variability With Morbidity and Death in the Pediatric Intensive Care Unit. Pediatrics. 2006;118(1):173-9.
31. Hirshberg E, Larsen G, Van Duker H. Alterations in glucose homeostasis in the pediatric intensive care unit: Hyperglycemia and glucose variability are associated with increased mortality and morbidity. Pediatric Critical Care Medicine. 2008;9(4):361-6.