Clinical Symptoms, Pathogen Spectrum, Risk factors and Antibiogram of Suspected Neonatal Sepsis cases in Tertiary Care Hospital of Southern Part of Nepal: A Descriptive Cross-sectional Study

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ABSTRACT

Introduction: Neonatal mortality rate is highest in sub-Saharan Africa and Southern Asia region. The present study is undertaken to find out the prevalence of neonatal sepsis, recognize bacterial pathogens, neonatal risk factors, major symptoms, and their antibiotic sensitivity pattern in neonates in tertiary care hospital in southern Nepal.

Methods: A descriptive cross-sectional study was carried out in a tertiary care hospital from 2nd January 2017 to 20th February 2018 after approval (Ref: 125/2016-17). The sample size was calculated and convenience sampling was done. Data were collected from hospital records and microbiology laboratory and analysed by Statistical Package for Social Sciences.

Results: Out of 1200 clinically suspected cases, early-onset neonatal sepsis was seen in 290 (79.89%). A positive culture was seen in 363 (30.25%) in which maximum bacterial growth was found in 254 (69.98%) males. Preterm gestational age was seen in 265 (73%), low birth weight in 284 (78.23%), a vaginal delivery mode in 279 (76.90%), and delivery in hospital in 232 (63.91%). Likewise Staphylococcus aureus in 229 (63.08%) was found maximum followed by Klebsiella pneumoniae in 48 (13.22%). The major symptom observed was Respiratory distress in 245 (20.41%) while culture positive was seen in poor cry in 94 (53.10%). Mainly effective antibiotics against Gram-positive and gram-negative organisms were Linezolid in 250 (94%) and Imipenem in 46 (90.19%), whereas Penicillin-G in 254 (99.21%) and Ampicillin in 38 (94.74%) found resistance towards organisms respectively.

Conclusions: The high prevalence of neonatal sepsis in our study reflects a huge challenge to reduce the neonatal mortality rate to 12 by 2030 of Sustainable Development Goals. Bacterial isolates exhibited higher resistance towards commonly used antibiotics.

Keywords: antibiotics; bacterial spectrum; blood culture; neonatal sepsis.

INTRODUCTION

National Neonatal Mortality rate (NMR) was 21 per 1000 live births and 30 in province two.1 Neonatal sepsis is usually divided into early-onset neonatal sepsis (EONS) ≤ 72 hours of life and late-onset neonatal sepsis (LONS) ≥ 72 hours to four weeks of life.2,3 The management of neonatal sepsis, the commonest cause, of Neonatal mortality in developing countries is chiefly dependent upon the causative organism, onset of sepsis, site of infection, and related neonatal risk factors.4 The immediate treatment with limited information is very challenging to meet the target of

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Sustainable Development Goals-3 (SDG-3) for Nepal. This requires additional data for developing countries like Nepal due to regional variation.

The study aimed to find out the prevalence of neonatal sepsis in relation to neonatal risk factors along with Antibiotic Sensitivity Pattern (ASP) of the aerobic isolates from neonates in tertiary care hospital in southern Nepal.

METHODS

This was a descriptive cross-sectional study conducted in the Paediatric ward and NICU from 2nd January 2017 to 20th February 2018 in National Medical College and Teaching Hospital (NMCTH) after approval from the Institutional Review Committee (IRC) of the college (Ref: 125/2016-17). NMCTH is a tertiary care hospital in the southern part of Nepal (province two). Total neonates admitted in the pediatric and neonatal wards were 2965. The present study included all the inborn and outborn neonates with symptoms of sepsis (≤28 days) while excluded those that don’t indicate sepsis clinically. All the information regarding age, sex, birth weight, gestational age, mode, and place of delivery, clinical sign, and symptoms were recorded with the help of the pediatric department and hospital records. Among 1200 suspected neonates, blood was collected and processed microbiology laboratory for isolation, identification, and culture sensitivity. The assortment was based on signs and symptoms as described by previous studies. Convenience sampling and the sample size was calculated using the formula:

\[
n = \frac{z^2 \times p \times (1-p)}{\varepsilon^2}
\]

\[
= (1.96)^2 \times 0.48 \times 0.52 \times 0.03^2
\]

= 1065, 40

= 1065

Where,

\(n\) = required sample size

\(Z\) = 1.96 at 95% Confidence Interval (CI)

\(p\) = prevalence of neonatal sepsis (48%)

\(\varepsilon\) = margin of error (3%).

The total sample size was calculated to be 1065. However, 1200 samples were collected for the study.

1-2 ml of blood was collected with aseptic precaution before administration of starting any antibiotic therapy and carefully transferred into a culture bottle containing Brain Heart Infusion (BHI) Broth immediately to assure the ratio (1:10).

The culture bottles were incubated at 37°C for 7 days aerobically and were observed each day for turbidity, hemolysis of red cells, gas bubbles, and clot formation. During incubation, the first, second, and third subcultures were done on solid media. The axenic isolates obtained from subcultured plates were identified subsequently by standard microbiological techniques like colony morphology, Gram-staining reactions, and biochemical reaction. The culture bottle did not show growth after 24hr were observed for 7 days before regarded as no growth. Antimicrobial susceptibility tests were performed of the bacterial isolates to some normally used antibiotics by the Kirby Bauer disk diffusion method and interpreted according to Clinical Laboratory Standards Institute (CLSI) guidelines. All antibiotic discs used were of Hi-Media, Mumbai, India. Staphylococcus aureus ATCC 25923 and Klebsiella pneumoniae ATCC 700603 were used as control organisms for antibiotic sensitivity testing.

All the data obtained were entered in the Microsoft Excel worksheet and was analyzed using the Statistical Package for the Social Sciences (SPSS) software version (22.0).

RESULTS

One thousand two hundred blood cultures of neonates were evaluated during the study period. Out of 1200 clinically suspected cases of neonatal sepsis, 1024 (84.33%) were early-onset and 176 (14.67%) were late-onset in which positive blood culture was found in 290 (28.32%) and 73 (41.47%) cases respectively. Neonates ages ranging from 1 to 28 days with a mean age of 2.69±4.39 days. The mode was equal to 1 day and median equal to 1 day. Among 1200 enrolled neonates 843 (70.25%) were male and 357 (29.75%) were female. The male and female ratio of this study was 2.3:1. The occurrence of neonatal sepsis was 363 (30.25%). The highest frequency of bacterial growth was seen in 254 (69.98%) male neonates; EONS in 290 (79.89%); low birth weight in 284 (78.23%); preterm gestational age in 254 (69.98%); delivery in hospital in 232 (63.91%) (Table 1).

### Table 1. Prevalence of positive blood culture in relation to different neonatal risk factors.

| Variables | EONS group n (%) | LONS group n (%) | Total n (%) |
|-----------|------------------|------------------|-------------|
| Gender    |                  |                  |             |
| Male      | 203 (55.92)      | 51 (14.04)       | 254 (69.98) |
| Female    | 87 (23.96)       | 22 (6.06)        | 109 (30.02) |
| Gestational age at birth |                |                  |             |
| Preterm (<37 weeks) | 212 (58.40) | 53 (14.60) | 265 (73) |
| Term (>37 weeks) | 78 (21.48) | 20 (5.51) | 98 (27) |
Table 1. Prevalence of positive blood culture in relation to different neonatal risk factors.

| Variables        | EONS group | LONS group | Total group |
|------------------|------------|------------|-------------|
| Birth weight     |            |            |             |
| <2500gm          | 232 (63.91)| 52 (14.32) | 284 (78.23) |
| ≥2500gm          | 58 (15.98) | 21 (5.78)  | 79 (21.77)  |
| Mode of delivery |            |            |             |
| Vaginal          | 225 (54)   |            | 279 (76.86) |
| Caesarean section| 65 (17.90) | 19 (5.23)  | 84 (23.14)  |
| Place of delivery|            |            |             |
| Home             | 110 (30.30)| 21 (5.78)  | 131 (36.09) |
| Hospital         | 180 (49.58)| 52 (14.32) | 232 (63.91) |

The frequent clinical symptoms observed at the time of admission were respiratory distress 245 (20.41%), fever 210 (17.50%), poor cry 177 (14.75%), and the maximum percentage of bacterial growth were seen in poor cry 94 (53.10%) (Figure 1).

Table 2. Distribution of isolated organisms.

| Organism isolated | *EONS n (%) | †LONS n (%) | Total n (%) |
|-------------------|-------------|-------------|-------------|
| Klebsiella        | 41 (14.13)  | 7 (9.58)    | 48 (13.22)  |
| Pseudomonas aeruginosa | 16 (5.51) | 5 (6.84) | 21 (5.79) |
| E. coli           | 14 (4.82)   | 3 (4.10)    | 17 (4.69)   |
| Enterobacter spp. | 4 (1.39)    | 2 (2.73)    | 6 (1.65)    |
| Proteus spp.      | 10 (0.34)   | 0 (0)       | 1 (0.27)    |

*EONS: Early-onset neonatal sepsis †LONS: Late-onset neonatal sepsis

+CONS: Coagulase-negative Staphylococcus

In the present study, the most effective antimicrobial agents against Gram-positive organism was Linezolid 250 (94.94%) whereas Penicillin-G 254 (99.21%) and Amikacin 190 (81.20%) were found resistant. For Gram-negative organisms, Imipenem 46 (90.19%), was highly sensitive while antibiotics such as Ampicillin 38 (94.74%) and 3rd generation cephalosporin were found resistance towards the isolates in our study. Antibiograms of gram-positive and gram-negative bacteria are shown in (Table 3) (Table 4) respectively.

Table 3. Antibiotic sensitivity profile of Gram-positive bacteria.

| Antimicrobial    | Staphylococcus aureus (n=229) | CONS (n=13) | Streptococcus spp. (n=1) |
|------------------|--------------------------------|-------------|--------------------------|
| Vancomycin (30mcg) | 193 (85.40) | 12/12 (100) | 25/28 (90.19) |
| Linezolid (30mcg)  | 210 (92.92) | 12/12 (100) | 27/28 (100)   |
| Penicillin-G (10U) | 0/225 (0)   | 0/10 (0)    | 2/21 (9.52)    |
| Amikacin (30mcg)   | 29/197 (14.72) | 11/12 (91.67) | 4/25 (16)     |
| Meropenem (10mcg)  | 132/169 (78.10) | 6/11 (54.54)  | 3/18 (16.67)  |
| Cefotaxime (30mcg) | 10/164 (6.09) | 3/9 (33.33)   | 2/19 (10.52)  |
| Levofloxacin (5mcg) | 20/173 (11.56) | 4/12 (33.33)  | 5/19 (26.31)  |
Table 4. Antibiotic sensitivity profile of gram-negative bacteria.

| Antimicrobials    | Klebsiella pneumoniae (n=48) | Pseudomonas aeruginosa (n=21) | E. coli (n=17) | Enterobacter spp. (n=6) | Proteus spp. (n=1) |
|-------------------|-------------------------------|-------------------------------|---------------|----------------------|------------------|
| Amikacin(30mcg)   | 23/47(48.93)                 | 16/19(84.21)                  | 5/8(62.50)    | 2/5(40)              | 0/1(0)           |
| Meropenem(10mcg)  | 19/39(48.71)                 | 16/17(94.11)                  | 5/9(55.55)    | 4/6(66.67)           | 1/1(100)         |
| Cefotaxime(30mcg) | 0/33(0)                      | 4/13(30.77)                   | 0/5(0)        | 0/6(0)               | 0/1(0)           |
| Levofoxacin(5mcg) | 33/43(76.74)                 | 14/18(77.78)                  | 12/17(70.59)  | 5/6(83.33)           | 1/1(100)         |
| Cefixime(5mcg)    | 2/33(6.06)                   | 1/7(14.29)                    | 1/5(20)       | 0/6(0)               | 0/1(0)           |
| Piperacillin(100mcg) | 8/48(16.16)            | 10/21(47.61)                  | 8/17(47.05)   | 0/6(0)               | 0/1(0)           |
| Imipenem(10mcg)   | 30/32(93.75)                 | 3/4(75)                       | 8/9(88.89)    | 4/5(80)              | 1/1(100)         |
| Ceftriazone(30mcg) | 4/36(11.11)                  | 3/10(30)                      | 0/5(0)        | 0/6(0)               | 0/1(0)           |
| Ceftazidine(30mcg) | 4/13(30.77)                  | 4/16(25)                      | 0/17(0)       | 0/3(0)               | 0/1(0)           |
| Ampicillin(10mcg) | 1/21(4.77)                   | *NT                           | 1/16(6.25)    | 0/2(0)               | 0/1(0)           |

*NT: Not Tested

**DISCUSSION**

The causative organisms associated with neonatal sepsis vary from place to place and the episode of the causative organism is dissimilar in different hospitals and even in the same hospital at different times. The NMR of Nepal is 21/1000 live birth, however, the NMR of Province 2 is thirty. In this study, the prevalence rate of neonatal sepsis was 30.25% which reflects a high incidence compared to other regions. This finding was approx similar to that of Jain et al. (28.30%), Shrestha et al. (30.85%) from the western and central part of Nepal, respectively and Li et al. (28.26%) from Shanghai, China but our finding was higher than previously reported by Gyawali et al. (15.1%), Pokhrel et al. (20.7%), Chapagain et al. (14%), Yadav et al. (16.9%), Ansari et al. (12.6%), Shrestha and Subedi et al. (6.1%) from central part Nepal, Aku et al. (17.3%) from Ghana, Mehar et al. (22%) from India. The majority of culture-positive sepsis was found in our study within Male neonates (69.98%) which is comparatively higher than various studies ranging from (52.3%-63.5%) but Kayange et al. reported the opposite.

The study has shown a male-female ratio of 2.3:1 similar to the other studies, but the result was lower in another study. Thus male babies were suspected to double of neonatal sepsis than female babies due to X-linked immune regulatory gene factor resulting in the host's vulnerability to infections in males. From the clinically suspected cases of EONS and LONS blood culture positive was found higher in LONS (41.47%) than EONS which is in harmony with the study of Kayange et al. (51.4%) but different with other studies.

The majority of culture-positive sepsis was found in our study within Male neonates (69.98%) which is comparatively higher than various studies ranging from (52.3%-63.5%) but Kayange et al. reported the opposite.

In the present study, the incidence of EONS (79.89%) was higher which is in agreement with previous finding (57.1%-91.39%) whereas, in the study of Chapagain et al. (83.3%), Yadav et al. (71.2%), Li et al. (52.79%), Kayange et al. (45.31%) prevalence of LONS was higher. Since causative agents in neonatal EONS acquired from mother during birth play role in early infection.

We find out preterm(73%) neonates are more susceptible to sepsis which is consistent with various authors’ findings in contrast to this finding term baby are more prone to sepsis. Birth of baby before 37 weeks of gestational age might have a poor capacity to increase neutrophil production in accordance to demand to overcome the problem associated with neonatal bacterial sepsis. Probably due to the unhygienic condition of the vagina during birth and carelessness about the safety.
We found S. aureus and K. pneumoniae was the most common isolate in neonatal sepsis accounting for 63.08% and 25.61% among total isolates. This finding was similar to the finding of other studies, but unlike in these studies, the etiological agent varies due to the environmental condition of the hospital, sanitation of medical personnel, and geographical area.

The single predominant S. aureus was found in both onset of sepsis as similar to the other study, put in contrast to this, a different organism was found in the different onset of sepsis. In our study the most effective antibiotics against major isolate S. aureus, CONS, and Streptococcus spp. were Linezolid and vancomycin similar to the previous study.

As observed from the current study, For Klebsiella pneumoniae and other Gram-negative bacteria meropenem, imipenem and Levofloxacin be the drug of choice for treatment of neonatal sepsis. Gram-negative isolates showed a high degree of resistance to commonly used antibiotics such as ampicillin, Piperacillin as well as 3rd generation Cephalexin. This study agreed with studies from Nepal. The liberal use of broad-spectrum antibacterials increases the risk of acquisition of pathogens by interfering with the development of normal flora.

CONCLUSIONS

Overall, Neonatal sepsis is a life intimidating condition. So, the knowledge of major symptoms, care about associated risk factors, prevalent etiological organism, and current effective antibiotics should be known. Respiratory distress was the major symptom and common risk factors were vaginal delivery in the hospital, birth weight less than 2.5 kg, and a gestational period of fewer than 37 weeks. We found S. aureus was the most common isolate in both onsets of sepsis. We strongly recommend medical personnel working in NICU should be trained and maintain hand hygiene with proper disinfection during the procedure and use of Linezolid and Imipenem against gram-positive and gram-negative bacteria respectively as compared to the broad-spectrum antibiotics which are more rampanty used nowadays. This vital information helps Neonatologist to manage and treat neonates with sepsis. Thus, reduction in mortality will reduce the NMR in the southern part along with overall in Nepal to meet the SDG-3.

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