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PATTERNS OF PRETERM NEONATAL DEATH AND ASSOCIATED FACTORS IN AYDER REFERRAL HOSPITAL NEONATAL UNIT FROM 2010- 2014 (FIVE YEARS RECORD REVIEW), TIGRAY REGION, NORTH ETHIOPIA

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ABSTRACT

Background: Worldwide prematurity and its complications are the leading cause of death among newborns accounting for 1 million deaths per year. In Ethiopia among the three main direct causes of neonatal death, prematurity and its complications account 37%. Therefore, this study aimed to assess patterns of preterm neonatal death and associated factors in Ayder referral hospital, North Ethiopia.

Methods: Institutional based retrospective cross sectional study was conducted among preterm neonates in Mekelle University, Ayder referral hospital, Neonatal intensive care unit between 2010 and 2014. A total of 475 preterm neonates were included in this study using a non probability purposive sampling technique. Descriptive, binary and multiple logistic regression analyses were performed using SPSS version 16 and a variable having $p < 0.05$ was considered as statistically significant variable in all tests. Finally the result was presented using texts, figures and tables.

Results: A total of 410 preterm neonates were included in this study and making a response rate of 86%. Of these, 225 were male. The proportion of preterm neonatal death is 15%. Hyaline membrane disease [AOR=12.5, 95%CI (5.5-28.8)], starting KMC [AOR=0.024, 95% CI (0.005-0.1)], NEC [AOR=5.7, 95% CI (1.02-32)] and Apnea [AOR= 10.7, 95% CI (3.7-30.9)] were the factors that predict for preterm neonatal death.

Conclusions: There is a significant proportion of preterm infants' death. Extreme prematurity, HMD, NEC and apnea were the factors that predict preterm infants' death. So, further revising strategies on risk reduction of preterm neonates' death should be considered.

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INTRODUCTION

The target of MDG 4 was a two-thirds reduction in under five mortality between 1990 and 2015. Remarkable progress has been made prior to 1990, with a halving in risk of death for children under five over 30 years. One important barrier to progress for MDG 4 was the failure to reduce neonatal deaths (deaths in the first four weeks of life). Five countries account for just over two million deaths, over half the total newborn deaths, and ten countries account two thirds of the total (Lawn et al., 2009) Worldwide, approximately 15 million babies are born prematurely each year.

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Over 60% of preterm deliveries worldwide occur in Sub Saharan Africa and South Asia. Prematurity is the leading cause of death among newborns, accounting for 1 million deaths per year (Nour et al., 2012 and Fanaroff et al., 2007). Approximately 42% of the under-5 mortality in Ethiopia is attributable to neonatal deaths. According to the UNICEF/WHO 2013 Report Neonatal mortality rate were 29 per 1000 live births in Ethiopia. Eighty nine percent of neonatal deaths are attributable to three causes, namely preterm birth complications (37%), severe infections (24%), and intrapartum related (28%) in Ethiopia (Mekonnen et al., 2014; FMOH of Ethiopia et al., 2014; UNICEF, 2013). Prematurity and its complications being the commonest cause of morbidity and mortality in neonates in Ethiopia there is much job that can be done both in the community level and

institutions. The higher institutions like teaching hospitals are expected to have well equipped NICU for care of sick premature newborns. Ayder referral hospital is one of the teaching and tertiary care levels in Northern Ethiopia. As it serves referrals from different newborn corners and second level NICU there are many premature infants. Therefore, this study aimed to assess Preterm neonatal deaths and associated factors among premature newborns in Ayder Referral hospital, North Ethiopia. The findings of this study might be useful for policy makers and NGOs working on preterm infants and also important as background or baseline information for researchers who are interested in these areas.

METHODS AND MATERIALS

The study was conducted in Ayder Referral hospital, Mekelle city, Tigray region, North Ethiopia which is found at 783 km from Addis Ababa. Since 2008, ARH has become a referral hospital. The hospital has different departments and delivers diversified health services. It has postgraduate training services. The NICU at ARH opened in December 2009 and had treated a total of 4500 neonates up to December 2014, around 10.5 % of who were premature (ARH unpublished data). This study presents data for premature neonates admitted to the NICU of Ayder Referral Hospital from 1 January 2010 to 30 December 2014 and followed from admission until discharge from the unit. Data were obtained from medical records using a collection format. Study was conducted on 16th-20th, May 2015. Institutional based cross-sectional retrospective study was used. All preterm neonates' medical history cards admitted in NICU of Ayder referral hospital were used as a study population. All complete preterm neonates' medical history cards who was admitted to NICU and the first admission of each newborn until his/her discharge or death were included in the study. Preterm neonates who had incomplete medical history cards and preterm neonates' medical history cards with major congenital anomalies incompatible with life were excluded from the study.

Measurements

The outcome variable for the study was Hospital death of the preterm neonate. Structured and pre-tested document review questionnaire was used to collect the information. It was first prepared in English and then translated to Tigrigna and then translated back for consistency. Information collected included socio-demographic characteristics of neonates, maternal and care characteristics: Maternal age, ANC, Twin pregnancy, use of antenatal corticosteroids (for GA<35 weeks), maternal illnesses (hypertension, bleeding in the last trimester, diabetes, heart disease and infection, including chorioamnionitis, pneumonia, urinary tract infection and HIV). Premature infant characteristics: Gestational age (GA), birth weight, Gender, length of hospitalization, morbidities including hyaline membrane disease (HMD), patent ductus arteriosus (PDA), neonatal sepsis, necrotizing enterocolitis (NEC), and intraventricular hemorrhage, feeding at discharge and conditions at discharge. The questionnaire was adapted by reviewing different literatures and considering the local situation of the study subjects (deFreitas *et al.*, 2012; Poets *et al.*, 2012; Sritipsukho *et al.*, 2007; Yusuf *et al.*, 2010; Worku *et al.*, 1999). Two medical interns who speak local languages were employed in the data collection process. One general practitioner was selected as a supervisor. Training was given to the data collector and supervisor for two consecutive days on

the objectives of the study, the contents of the questionnaire and particularly on issues related to the confidentiality of the responses and the rights of respondents. Five days prior to the data collection, a pre-test was conducted at mekelle hospital which is another hospital in the same city that is it is non study area in 2.5% of the sample size for completeness of the data collection format. After data collection, data was stored in a secured place to maintain confidentiality and backup of the data was stored in different areas not to lose the data. Each questionnaire was coded separately before analysis.

Statistically Analysis

The collected data was coded, entered, cleaned and analyzed using SPSS version 20.0. Descriptive statistics was used to describe Preterm neonatal deaths. Frequencies and percentages were used to present categorical data. Mean (\pm standard deviation) was used for normally distributed continuous data. To determine the preterm infant deaths for each Preterm infant deaths question, one point was given for correct response and zero point was given for incorrect response. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a logistic regression model to determine association levels of predictors to the outcome variables. Crude ORs of predictors with preterm infant death among preterm neonates were estimated using bivariate logistic regression analysis. A multivariate logistic regression analysis was used to estimate the adjusted OR of predictors and to control confounding factors. A variable having $p < 0.05$ was considered as statistically significant variable in all model. Before inclusion of predictors to the final logistic regression model, the multicollinearity was checked using $VIF < 10$ /Tolerance tests > 0.1 . The goodness of fit of the final logistic model was tested using Hosmer and Lemeshow test at a value of > 0.05 . Finally the results of the findings were presented using text, graphs and tables.

Ethical consideration

The study protocol was approved by the institutional ethical committee of Mekelle University, College of health Sciences (MUCHS). Support letters were also received from Mekelle Regional Health Bureau and local Office to conduct the study in the area and permission was obtained at each level. The respondents were told that the study offers an opportunity for the hospital to get more information about Preterm infant death and associated factors among them. Informed written assent and consent were obtained from the university before data collection. The respondents' privacy and right to anonymity and confidentiality was respected at all times.

Operational definitions

Neonatal sepsis: neonates who was diagnosed clinically (risk factors, symptoms and evidence from hematologic profile) and received treatment. Neonatal death: death in the first 28 days of neonatal age. Early neonatal death: death of a neonate in the first 6 days of age. Preterm neonate: neonate born before 37 completed weeks of gestation. Moderately premature: gestational age between 32 weeks and 36 weeks and 6 days. Very premature: gestational age between 28 weeks and 31 weeks and 6 days. Extremely very preterm: below 28 weeks. Hypothermia: axillary temperature below 36.5 °c and mild between 35-36.4 °c, moderate 32-34.9 °c and severe below 32 °c. low birth weight: neonatal birth weight below 2500 grams, it is

very low birth weight if the birth weight is below 1500 grams and it is extremely very low birth weight if it is below 1000 grams.

RESULTS AND DISCUSSION

During the study period 475 premature neonates was admitted to the neonatal unit. The records for 65 (13.6%) patients were not included in the study because 49 cards were lost from card room and 16 excluded based on the criteria; thus, the study population consisted of 410 premature neonates.

Maternal Characteristics

The median maternal age during the study period was 26.0 years (14 to 45). There were only 39(9.5%) mothers whose gestational age was below 35 weeks who receive antenatal dexamethasone. Among these 34 mothers took the full dose, i.e., 4 injections before delivery. Among the maternal illnesses maternal infection was the predominant illness (Table 1).

infants were the most predominant followed by very premature and extremely premature infants. The median length of stay in the NICU was 9 days (1day-91days). Above 95% of the preterm neonates were admitted with axillary temperature below 36.5⁰c (Table 2).

Mortality in the Preterm Neonates

Sixty (14.6%) of the respondents were died in the hospital, resulting in 85.4 % survival rate, which was directly related to the gestational age. accordingly, 14 out of 20 (70%) of the extremely premature infants, 22.6% of very premature infants and only 5.6% of the moderately premature infants died in the hospital. Mortality decreased significantly as the GA increased, and the deaths of extremely premature infants were concentrated in the early neonatal period. It was observed that all of the preterm neonates (n=60) died during the neonatal period that is within the first 28 days and of these 86.4% (n=51) died in the early neonatal period (first 6 days of life) (Figure 1).

Table 1. Characteristics of Maternal care among Preterm infant deaths, Ayder Referral Hospital, North Ethiopia, 2015(N=410)

Variables	Jan2010- Dec2010 No (%)	Jan2011-Dec2011 No (%)	Jan2012-dec2012 No (%)	Jan2013- Dec2013 No (%)	Jan2014-Dec2014 No (%)	Total(n)
Maternal age						
<20	4 (8.7)	8 (17.4)	5(10.9)	15(32.6)	14(30.4)	46
20-34	36(12.0)	54(17.9)	60(19.9)	72(23.9)	79(26.2)	301
≥35	5(7.9)	7(11.1)	14(22.2)	13(20.6)	24(38.1)	63
ANC visits	40(10.6)	61(16.1)	77(20.4)	91(24.1)	109(28.8)	378
Twin pregnancy	13(8.7)	25(16.8)	28(18.8)	37(24.8)	46(30.9)	149
Antenatal corticosteroids	3(7.7)	6(15.4)	5(12.8)	11(28.2)	14(35.9)	39
Mother illness						
Hypertensive disorder	2(3.8)	11(20.8)	7(13.2)	14(26.4)	19(35.8)	53
3 rd trimester bleeding	-	5(17.9)	8(28.6)	9(32.1)	6(21.4)	28
Maternal infection	7(11.1)	14(22.2)	13(20.6)	12(19)	17(27.0)	63

ANC= antenatal care

Table 2. Characteristics of the preterm neonates and conditions at Discharge, Ayder Referral Hospital, North Ethiopia, 2015(N=410)

Variables	Jan2010-Dec2010 No (%)	Jan2011-Dec2011 No (%)	Jan2012-dec2012 No (%)	Jan2013-Dec2013 No (%)	Jan2014-Dec2014 No (%)	Total(n)
Gestational Age in weeks						
<28 weeks	-	2(10)	3(15)	6(30)	9(45)	20
28-31wks	16(11.3)	21(14.9)	22(15.6)	38(27)	44(31.2)	141
32-36+5	29(11.8)	46(18.7)	52(21.1)	56(22.8)	63(25.6)	246
Birth weight(grams)						
≤999	2(15.4)	2(15.4)	1(7.7)	5(38.5)	3(23.1)	13
1000-1499	12(10.8)	17(15.3)	19(17.1)	30(27)	33(29.7)	111
1500-2499	29(11.5)	41(16.3)	44(17.5)	61(24.2)	77(30.6)	252
≥2500	2(5.9)	9(26.5)	15(44.1)	4(11.8)	4(11.8)	34
SGA	4(13.3)	1(3.3)	6(20)	7(23.3)	12(40)	30
Sex						
Male	25(11.1)	39(17.3)	43(19.1)	57(25.3)	61(27.1)	225
Female	20(10.8)	30(16.2)	36(19.5)	43(23.2)	56(30.3)	185
Morbidities						
HMD	15(12.3)	19(15.6)	17(13.9)	32(26.2)	39(32)	122
Sepsis	40(12.2)	54(16.5)	53(16.2)	79(24.1)	102(31.1)	328
NEC	8(42.1)	2(10.5)	1(5.3)	3(15.8)	5(26.3)	19
Jaundice	13(13.7)	18(18.9)	20(21.1)	17(17.9)	27(28.4)	95
Hypoglycemia	7(14.6)	12(25)	12(25)	10(20.8)	7(14.6)	48
Apnea	3(7.9)	4(10.5)	6(15.8)	12(31.6)	13(34.2)	38
Discharge condition						
Improved	36(10.9)	58(17.5)	64(19.3)	79(23.9)	94(28.4)	331
Against	2(10.5)	3(15.8)	4(21.1)	5(26.3)	5(26.3)	19
Death	7(8.7)	8(8.7)	11(8.7)	16(26.1)	18(47.8)	60

SGA=small for gestational age, HMD= hyaline membrane disease, NEC= necrotizing enterocolitis, Against= discharged against medical advice

Preterm Neonatal Characteristics

A total of 410 preterm neonates were included in the study and making a response rate of 86%. Of these, 225 of them were males. The mean for gestational age of the premature neonates was 32.8 weeks (27.0 to 36 weeks and 5days) and the median birth weight was 1,700g (700-3900 g). Moderately premature

Factors significantly associated with preterm neonatal death

Kangaroo mother care (KMC), necrotizing enterocolitis (NEC), Apnea, sepsis and hyaline membrane disease (HMD) were the factors associated with Preterm neonatal death in the bivariate logistic regression analysis. The multivariate logistic

regression analysis showed that, respondents who have had HMD were found to be 12.5 times more likely to have Preterm infant death than who did not have [AOR=12.5, 95% CI (5.5, 28.8)]. Those respondents who had NEC were found to be 5.7 times more likely to have Preterm neonatal death than who did not have [AOR= 5.7, 95% CI (1.02, 32)]. Respondents who had Apnea were found to be 10.7 times more likely to have Preterm neonatal death than who did not have [AOR= 10.7, 95% CI (3.7, 30.9)]. Respondents who used KMC were found to be 99.97% less likely to have Preterm neonatal death than who did not use KMC [AOR= 0.024, 95% CI (0.005, 0.1)] (Table 3).

study and 34 took complete doses and 5 mothers took less than 4 doses. In retrospective study done in the state of Qatar on the outcome of 28wk+1day to 32+0 weeks gestation babies on data covering a five year period 86 % of the mothers had received antenatal steroids.[9]In a cross-sectional retrospective study on premature infants in one referral Hospital Sao Sebastiao NICU in Vicosa Brazil, on a data collected of 297 preterm neonates antenatal corticosteroid use was (57.4%), (deFreitas *et al.*, 2012). The very low dexamethasone intake can be explained by lack of proper training of professionals working in the health centers because the referrals of all patients from health center in this study did not show any

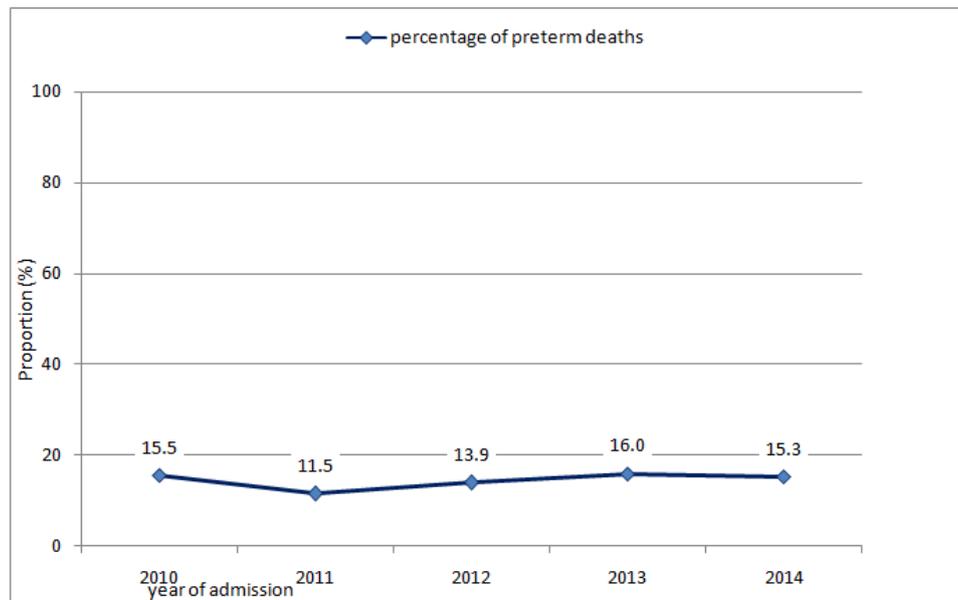


Fig.1. Preterm neonatal death by year of admission in Ayder Referral Hospital, North Ethiopia, 2015

Table 3. Factors significantly associated towards Preterm neonatal death, Ayder Referral Hospital, North Ethiopia, 2015(N=410)

variable	Survival status of preterm neonates		COR(95%CI)	AOR(95%CI)	P- value
	Death	Alive			
HMD					
NO	13	275	1	1	
YES	47	75	13.26(6.8-25.7)	12.5(5.5-28.8)	0.001**
NEC					
NO	51	340	1	1	
YES	9	10	6(2.3-15.4)	5.7(1.02-32)	0.047**
Apnea					
NO	36	366	1	1	
YES	24	14	16(7.6-33.6)	10.6(3.7-30.9)	0.001**
Sepsis					
NO	1	81	1	1	
YES	59	269	17.7(2.4-130.2)	6.7(0.81-55.4)	0.078
KMC					
NO	58	199	1	1	
YES	2	151	0.045(0.01-0.18)	0.024(0.005-0.1)	0.001**

**Tests were considered significant if P value is <0.05. KMC= kangaroo mother care, NEC= necrotizing enterocolitis, HMD= hyaline membrane disease, COR= Crude odds ratio, AOR= Adjusted odds ratio

DISCUSSION

The antenatal corticosteroid use in mother whose gestational age is less than 35 weeks is very low in this study as compared to other similar studies in other countries (deFreitas *et al.*, 2012; Hyagriv *et al.*, 2012 and Parappil *et al.*, 2010) Of the 410 premature neonates studied, only 39 (9.5%) of the mothers of these preterm neonates received dexamethasone in this

documentation on antenatal steroids use, poor documentation from hospitals and late presentation during labor of the pregnant mothers. Antenatal corticosteroid use has been shown to be protective in different studies but this study did not show any benefit over those who took it. This was explained by the low intake. Maternal infections were predominantly found in mothers of the preterm neonates in this study, and this is consistent with the major clinical risk factors for preterm birth.

Systemic and genital tract infections are associated with preterm birth (Hyagriv *et al.*, 2012) Among the maternal infections documented in the study population HIV/AIDS was the most common maternal illness followed by chorioamnionitis, UTI and pneumonia in their respective order. Notably, there was large number of preterm neonates with hypothermia 396 (96.5 %). This was even higher than the report in another tertiary hospital in Ethiopia around 90% (Worku *et al.*, 2010). Neonatal hypothermia has been associated with increased risk of infection, coagulation defects, acidosis, delayed fetal to newborn circulatory adjustment, hyaline membrane disease, brain hemorrhage, increased oxygen consumption, and increased mortality (Silverman *et al.*, 1958; Klaus *et al.*, 2013 and Mullany *et al.*, 2010). This huge problem among preterm neonates is due to poor transport breaching the warm chain system from health centers and another hospital to Ayder Referral hospital but it remains in need of detailed explanation. KMC was found significantly protective against death in this study population which was similar to other studies. KMC is started as a way of reducing low birth weight mortality in black lion hospital (Lakew *et al.*, 2014). KMC is one of the interventions proven to be a safe alternative to conventional neonatal care in resource-limited settings. KMC is a package of care including skin - to -skin contact, exclusive breastfeeding, and support to the mother child Dyad, and avoiding mother -child separation (Conde-Agudelo *et al.*, 2011).

The diagnosis of neonatal sepsis was made based on clinical evidence in 331(80.5%) of preterm neonates and only one neonate was proved to have neonatal sepsis by the gold standard test, blood culture. Except for three preterm neonates all the rest neonates were started on empirical antibiotics, once they were clinically diagnosed to have sepsis before blood sample was taken for Culture and Sensitivity. The culture intake was much less than the study done in Black Lion hospital in Addis Ababa, Ethiopia. The reason for the delay of sample for Blood Culture in black lion hospital was the Bacteriology Unit closes after the Off Duty hours and weekends, and sometimes the attendants don't pay for the Investigation soon enough. Apparently the admitting physicians are obliged to start empirical antibiotics, to avoid any delay of life saving treatment. The reason is similar in this hospital too (Yusuf *et al.*, 2010). The death in preterm neonates was inversely related with birth weight and gestational age and this is consistent with other studies from different countries (deFreitas *et al.*, 2012; Sritipsukho *et al.*, 2007; Hyagriv *et al.*, 2012; Carlo Waldemar *et al.*, 2011 and Lee *et al.*, 2008). It was observed that 14.6% of the population died in the hospital, resulting in 85.6% survival rate, which was directly related to the GA.

The death rate was low in this study even lower than what was found in Black lion hospital among low birth weight neonates which was 32.8%, (Worku *et al.*, 1999). This was explained by that there were patients who went against medical advice in which they went when the neonate became critically ill for fear of hospital death because transportation is costly, poor documentation, poor handling of registration books. It showed that preterm neonates diagnosed to have HMD was 12 times at increased risk of death than those who had no such diagnosis [Adjusted odds ratio (AOR) =12.5, 95%CI 5.5-28.8]. This high risk of death from hyaline membrane disease can be explained by the low use of Antenatal steroids, no post-natal surfactant use, and modes of ventilation being poor. Optimal results

depend on the availability of experienced and skilled personnel, care in specially designed and organized hospital units, proper equipment, and lack of complications such as severe asphyxia, intracranial hemorrhage, or irremediable congenital malformation. Surfactant therapy has reduced mortality from RDS by approximately 40% (Carlo Waldemar, 2011). It was observed that neonates diagnosed to have Apnea had increased risk of death taking those neonates with no such diagnosis as reference category (AOR =10.7, 95% CI 3.7-30.9). The absence of apnea monitors and delayed detection may be the contributory factors but it needs explanation for the increased risk of death. Necrotizing enterocolitis showed also to have increased risk of death (AOR= 5.7, 95% CI 1.02-32). NEC was similarly associated with high risk of death in one study in Brazil (deFreitas *et al.*, 2013).

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