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OUTCOME OF APNEA MANAGEMENT WITH AMINOPHYLLINE AND ASSOCIATED FACTORS AMONG PRETERM INFANTS ADMITTED TO PUBLIC HOSPITALS, ADDIS ABABA, ETHIOPIA 2024 - RETROSPECTIVE STUDY.

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A THESIS TO BE SUBMITTED TO THE POST GRADUATION STUDIES, ADDIS ABABA UNIVERSITY COLLAGE OF HEALTH SCIENCES NURSING AND MIDWIFERY DEPARTMENT, IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN NEONATAL NURSING

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Declaration

This thesis by **ABENEZER ADMASU**, I declare that this is an original thesis has been written by me and has not been submitted for any previous degree. This thesis is accepted in its present form by the Advisors and Board of examiners as satisfying thesis Thesis requirement for the Degree of Master of Science in Neonatal Nursing.

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ABBREVIATIONS AND ACRONYMS

AOP	Apnea of prematurity
AGA	Appropriate for Gestational Age
ANC	Antenatal Care
CI	Confidence Interval
CS	Cesarian Section
GMH	Gandhi Memorial Hospital
ELBW	Extremely Low Birth Weight
KMC	Kangaroo Mother Care
LBW	Low Birth Weight
NICU	Neonate Intensive Care Unit
PO	Per Oral
SD	Standard Deviation
SGA	Small for Gestational Age
SPH	St. Peter Hospital
SPHMMC	Saint Paul's Hospital Millennium Medical College
SVD	Spontaneous Vaginal Delivery
TASH	Tikur Anbessa Specialized Hospital
TID	Three times In Day
VLBW	Very Low Birth Weight
WHO	World Health Organization
PMA	Post Menstrual Age

Table of contents

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Background: Prematurity (birth before 37 weeks of gestation) can lead to serious complications. One such complication is apnea (a temporary cessation of breathing) and this complication can be fatal. Management of apnea with Aminophylline among preterm babies has shown a promise by stimulating the respiratory center and improving respiratory function. But evidences on the outcome of aminophylline use for treatment of apnea in preterm babies is scanty in developing countries, like Ethiopia.

Objective: This study aimed at assessing the outcome of aminophylline use for management of apnea and associated factors among preterm infants admitted to public hospitals, Addis Ababa, Ethiopia 2024.

Methods: A facility-based cross-sectional study was conducted among 422 randomly selected preterm infants who were admitted from Jan 1, 2021- Dec31, 2023. Using a checklist, data were extracted by reviewing charts. The data were then cleaned, coded, and entered into EpiData 4.6, and subsequently exported to SPSS version 27 for analysis. Variables with a p-value of <0.25 on bi-variable analysis were entered into a multi-variable logistic regression analysis. Factors with a p-value of <0.05 were declared statistically significant.

Result: A total of 415 neonate charts were reviewed successfully. Although the majority of preterm infants who received Aminophylline for the management of apnea showed improvement, a significant proportion (32.2%) of them did not survive. The odds of death were higher in preterm neonates with: a birthweight of less than 1 kg (AOR = 18.9, 95% CI [4.6, 77.9]), a birthweight between 1 kg and 1.5 kg (AOR = 2.8, 95% CI [1.1, 7.1]), pulmonary hemorrhage (AOR = 3.7, 95% CI [1.2, 11.1]), apnea episodes after the initiation of Aminophylline (AOR = 2.5, 95% CI [1.2, 5.1]), those who did not receive nasal oxygen therapy (AOR = 53.1, 95% CI [24.0, 117.3]), and hypoglycemia (AOR = 3.3, 95% CI [1.5, 7.4], p = 0.003) compared to their respective counterparts. Lastly, premature neonates who were treated with Aminophylline for less than 10 days had 4.8 times higher odds of death compared to those treated for 10 days or more (AOR = 4.8, 95% CI [2.0, 11.4]).

Conclusion and recommendation: These findings highlight critical risk factors associated with mortality in preterm infants receiving Aminophylline and underscore the need for targeted interventions to improve survival outcomes. Based on these findings, we recommend implementing enhanced care protocols for extremely/very low birthweight neonates, prioritizing early detection and management of pulmonary hemorrhage, reviewing aminophylline treatment protocols, ensuring universal access to nasal oxygen therapy, optimizing hypoglycemia management protocols, and conducting further research in these areas.

Keywords: Preterm, Apnea of Prematurity, Aminophylline

1. INTRODUCTION

1.1. Background

Preterm birth defined as delivery of a baby before 37 completed weeks of pregnancy. Approximately 15 million babies are born preterm annually worldwide. Preterm birth is the leading cause of death among children. Burden is particularly high in low- and middle-income countries. Preterm birth rates are rising in many countries.(1) Prematurity profoundly affects breathing, making it highly irregular, with frequent pauses or apneas. This respiratory instability is secondary to the immature development of the respiratory network as well as the underdevelopment of the lungs (2)

The percentage of preterm births worldwide in 2014 was 10.6%. Apnea Of Prematurity (AOP) is one of the commonest respiratory problems of preterm newborns. It affects almost all newborn born less than 28 weeks of gestational age and up to 20% of neonate born before 34 weeks of gestational age(3). Apnea of prematurity (AOP), defined as cessation of breathing by that lasts for more than 20 seconds and/or is accompanied by hypoxia or bradycardia, is one of the developmental disorders that preterm infants face. AOP is caused by the immaturity of the central nervous system. AOP improves as gestational age increases. AOP affects oxygenation and heart rate, potentially impacting neurodevelopment. Incidence of AOP decreases with higher gestational age and birth weight.(4)

AOP is divided into three categories based on its cause: central (most frequent), obstructive, and mixed. Immature medullary respiratory control centers are the cause of central apnea. The causes of obstructive apnea include nasal occlusion, reflex laryngospasm, obstruction of airflow, and neck flexion that opposes the hypopharyngeal soft tissues. Combining central and obstructive apnea results in mixed apnea. If an apnea of any kind lasts for a long time, it might result in hypoxemia, cyanosis, and bradycardia. Bradycardia and apnea can also happen at the same time, suggesting that a single central mechanism could be in charge of both conditions. (5,6)

Central apnea is characterized by total cessation of inspiratory efforts with no evidence of obstruction. In obstructive apnea, the infant tries to breathe against an obstructed upper airway, resulting in chest wall motion without airflow through the entire apneic episode. Mixed apnea consists of obstructed respiratory efforts, usually following central pauses.(7)

Since there are numerous potential causes of apnea, the identification of the underlying pathology and investigation results will determine the course and type of treatment for the illness. There are two approaches to managing AOP: non-pharmacological and pharmacological. Using Continuous Positive Airway Pressure (CPAP), tactile stimulation, and avoiding reflexes that may trigger apnea (like

aggressive pharyngeal suctioning and positioning the neck in excessive flexion or extension) are all part of the non-pharmacological method to treating apnea. The primary goal of pharmacological treatment is to prevent or treat apnea using Methylxanthine compounds such as caffeine, theophylline, and aminophylline. The first-line treatment of choice for AOP in poor nations is aminophylline. Greater doses of aminophylline and early initiation may result in improved outcome (7,8).

1.2. Statement of the problem

The occurrence of apnea varies according to the neonate's gestational age (GA). Of those born before 28 weeks of GA, virtually all will develop apnea; of those born between 28 and 30 weeks of GA, 85% will do so; and up to 20% of those born before 34 weeks of GA may develop an apnea (7).

Extended periods of severe apnea, lasting more than 20 seconds, are typically linked to bradycardia or desaturation. These conditions can disrupt brain hemodynamics and potentially impact the course of neurodevelopment. AOP has both short- and long-term consequences (3). The short-term consequences are desaturation and bradycardia. Prolonged bradycardia and apnea can lower blood pressure throughout the body and cause cerebral hypoperfusion, which can exacerbate hypoxic-ischemic harm to the developing brain (9,10).

In the long run, a higher number of AOP days is linked to neurodevelopmental disability, including cerebral palsy and blindness. Preterm newborns are more likely to have adverse outcomes, including death, if AOP is more common and severe. Because, repeated episodes of hypoxia and bradycardia result in cerebral dysfunction (3,11).

To prevent the short- and long-term effects of AOP, methylxanthines are effective therapies for preterm apnea. Methylxanthines have the ability to lessen the requirement for artificial breathing by reducing hypoxia and apnea episodes (12). However, methylxanthines are not free of adverse effects. When levels are too high, they might cause seizures, tachycardia, cardiac dysrhythmias, and difficulty eating. Infants born with extremely low birth weights may also have mild diuresis and delayed stomach emptying. Methylxanthines also increase energy consumption, which may cause premature newborns to grow less rapidly (13,14).

Two common methylxanthine group medications used to treat and prevent preterm apnea are aminophylline and caffeine. Additionally, aminophylline is a common medication used for AOP in many developing countries like Ethiopia, due to concerns about cost and availability. While aminophylline is more effective than caffeine in managing AOP, caffeine is thought to be safer and have less side effects (3). Aminophylline is exclusively administered intravenously; caffeine can be administered intravenously and orally. While aminophylline should be taken three times a day, caffeine is administered once a day (15).

Nevertheless, there is a paucity of studies on the effectiveness of aminophylline for the treatment of apnea of prematurity in developing countries like Ethiopia. Study among preterm neonate and related to apnea treatment of aminophylline associated factors especially those conducted are limited not only in our country but also in Africa. The results of this study will provide valuable insights into the use of

aminophylline in the treatment of apnea of prematurity in Ethiopian neonates and may help improve the standard of care for these infants. Thus, this study aims to fill that gap by assessing the effectiveness of aminophylline in treating apnea of prematurity and its related variables among preterm newborns hospitalized to public hospitals in Addis Ababa, Ethiopia.

1.3. Significant of the study

This research aims to systematically investigate the outcomes of apnea management with Aminophylline among preterm infants in public hospitals in Addis Ababa, Ethiopia. By examining the associated factors and effectiveness of Aminophylline, this study seeks to add value to the optimization of apnea management strategies in Ethiopian public hospitals. In other words, it attempts to fill the gap in knowledge about the effectiveness of Aminophylline for the treatment of apnea among premature neonates in developing countries like Ethiopia.

By identifying the factors associated with the outcomes of apnea of prematurity treated with Aminophylline, this research will provide critical insights into the effectiveness of current treatment protocols. The findings have the potential to inform and optimize clinical practices, enhance the survival rates and well-being of preterm infants, and guide healthcare policy in Ethiopia. Additionally, this study will contribute valuable knowledge to the global understanding of apnea management in preterm neonates, particularly in developing countries, and may serve as a foundation for future research and improvements in neonatal care.

2. LITERATURE REVIEW

2.1. sociodemographic of apnea of prematurity

Department of Pediatrics, The University of Virginia School of Medicine Number and duration of apnea events decrease with increasing gestational age. Apneas with bradycardia and desaturation are more frequent in infants <31 weeks gestational age. Apnea events are increased in some infants before diagnosis of late-onset septicemia and necrotizing enterocolitis. Many infants continue to experience short apnea events before discharge home.(16)

Department of Pediatrics, West China Second University Hospital, Seven percent of neonates born at 34- 35weeks gestation,15% at 32-33 weeks gestation, 54% at 30-31weeks and nearly all infant born at less than 29 weeks gestation or less than 1000g exhibit AOP.(3)

The overall incidence of apnea of prematurity was estimated to be 25% in study done in India (17). In study done in Nigeria public hospital apnea was detected in 75.5% of preterm babies had at least one episode of apnea.(18)

2.2. outcome of Aminophylline using for apnea of prematurity

Fifty-two neonates were randomized for the study in Iran and all of them completed its Primary out comes were clearly different between the two groups.
Out of the 16 infants (61.5 percent) in the control group, only 2 (7.7 percent) had developed apnea afte r being placed in the aminophylline group ($P < 0.001$).16 babies (61.5 percent) who did not receive am inophylline experienced cyanosis, while three and four newborns (11.5 percent and 15.4%, respectivel y) in the aminophylline group experienced bradycardia ($P < 0.001$)(19).There are difference in comparative effectiveness of caffeine and aminophylline in preventive and treatment of AOP as many are in favor of caffeine but some study show equal effectiveness or aminophylline being more effective than caffeine. In study done in South Africa and Pakistan caffeine was more effective than aminophylline (20,21) and study done in Indonesia there was slight effectiveness of aminophylline as compared to caffeine.(22) and study which was done in India showed equal effective of both drugs(23).

2.2.1. Factors affecting effectiveness of aminophylline in Apnea of prematurity

This study evaluates predictive factors for the efficacy and safety of theophylline therapy for extubating in Japanese infants with apnea of prematurity (AOP) after weaning from mechanical ventilation. A total of 100 infants were evaluated, and 66.0% had effective theophylline therapy. The study found that gestational age at birth was significant for predicting the efficacy of theophylline, with a cut-off value of 31.1 weeks old. Adverse reactions were identified in 21 (21.0%) infants, and the number of days of theophylline administration from birth was associated with an increased risk of adverse reactions after

theophylline administration. The study concludes that physicians should be aware of the possibility that theophylline may not produce therapeutic effects for extubating in infants aged less than 31.1 weeks old, and that adverse reactions can easily develop when theophylline is administered soon after birth. (24).

South African Family Practice, there are factors which can influence the efficacy of aminophylline in preventing AOP. Gestational age, birth weight at the initiation of aminophylline, and serum theophylline concentration were shown to act as predictive factors for the efficacy of aminophylline treatment of AOP(20).

2.2.2 Monitoring of neonate on Aminophylline

Hospital, Mahidol University, Bangkok, Thailand As the drug therapeutic window of aminophylline is narrow and adverse effect are usually related to increased drug concentration in the neonate blood`, serum level of aminophylline should be followed for early detection of the adverse effect caused by the drug and early intervention.(25)

On study done in China apneic episodes in neonates were monitored by Electro Cardiography (ECG) monitor and pulse oximetry before and after aminophylline administration.(26)

2.2.3 Duration and dose of Aminophylline for apnea of prematurity

In Iranian study 5mg/kg aminophylline intravenous was used as loading dose and followed by 1.5mg/kg every 8 hourly as maintenance dose administered for the first 10 days of life.(12)

In study done in China the loading dose was 5 mg/kg followed by maintenance dose of 3mg/kg/day divided in three doses a day. If there were no apnea episodes for seven consecutive days' medication was discontinued. (27).

In China e clinical feature of infants who received aminophylline as treatment for AOP over period of 8 - 12 days and identified factors associated with efficacy and safety of aminophylline treatment.(26)

2.3. Adverse effect with the use of Aminophylline

Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand A randomized controlled trial comparing serum theophylline levels and side effects between two aminophylline regimens in preterm infants was conducted. The study involved 22 infants of gestational age less than 35 weeks and birthweight less than 2,000 grams who required aminophylline treatment or prophylaxis for apnea of prematurity. The infants were randomly allocated to one of two groups: one received an intravenous aminophylline loading dose at 5 mg/kg and then maintenance at 6 mg/kg/day, and the other received a loading dose at 8 mg/kg and maintenance at 4 mg/kg/day. Serum theophylline levels were measured at

2 to 3 hours after the loading dose and before the sixth maintenance dose. Common side effects of aminophylline include tachycardia, diuresis, hyperglycemia, irritability, and feeding intolerance(28)

In study done in Thailand on 25 neonates given aminophylline for AOP, tachycardia and feeding intolerance were observed in 44% and 24% in neonates respectively after achieving therapeutic level of theophylline.(29) In China Among 206 neonates 53(25.73%) developed adverse effect. The adverse reactions observed included gastrointestinal reaction, hypoglycemia and tachycardia; with 23 newborn had more than one adverse reaction.(26) In study done in Japan on 100 neonates adverse reaction were identified in 21 (21%) neonates among them 15 had abdominal fullness, four had tachypnea, two had vomiting one had hypoglycemia and one had nervous irritability and adverse effects were more common in those who received aminophylline for longer duration and higher serum level of the drug.(30)

2.7 Neonatal factor prematurity related apnea

The records of 25,154 live born babies at King George V Memorial Hospital in the six years 1974-1979. Recurrent apnea occurred in 1% of live born babies. The highest incidence of recurrent apnea is at 30-31 weeks gestation. Incidence of apnea increased with decreasing gestational age. Apnea usually commenced in the first 2 days of life. Apnea duration was longer in babies with lower gestational age. Immaturity plays a major causative role in recurrent apnea.(31)

The Addis Ababa, Ethiopia study found that RDS (45%), sepsis, pneumonia and meningitis (combined as neonatal infections, 30%) and asphyxia (14%). followed by those between 28 and 31 weeks (54%), 32 and 34 weeks (18%) and in those 34 to 36 weeks (8%). Hyaline Membrane Disease 44.7%, pulmonary hemorrhage or diffuse alveolar hemorrhage in 39%, and meconium aspiration in 5.9%. The study showed that hypothermia is a common condition among preterm (69%)(32)

2.8. Maternal factor prematurity related apnea

Polish Society of Gynecologists and Obstetricians Hospital of Fujian Medical University The study involved 986 pregnancies with preterm delivery and 1094 live born preterm infants study investigates the impact of advanced maternal age between on the maternal and neonatal outcomes of preterm pregnancies. Multivariate analysis that mothers of advanced age were more likely to suffer preterm birth, placenta Previa, preeclampsia, gestational diabetes mellitus, and postpartum hemorrhage, but less likely to suffer multiple gestation. In terms of neonatal outcomes, advanced maternal age was associated with a decreased rate of low birthweight. According to the exclusion criteria, 986 patients were included in the study with 230 (23.33%) women at the age of ≥ 35 years and 756 (76.67%) women at the age of 18–34 years(33)

Canadian Neonatal Network retrospective cohort study better understanding of the duration of the beneficial effects of antenatal corticosteroids is of major importance because it may affect the decision to administer antenatal corticosteroids in cases in which the risk of preterm birth within the next 7 days is low.(34)

Retrospective Cohort Study American College of Obstetricians and Gynecologists the study was a retrospective cohort study of all singleton pregnancies, delivered between 22- and 29-weeks' gestation between 2010 and 2015 admitted for preterm delivery. There were 271 eligible deliveries, which included 128 cesarean deliveries and 143 vaginal deliveries. The overall composite neonatal morbidity occurred in 202 of the 271 (74.5%) deliveries and mortality occurred in 26 of the 271 (9.59%) delivery. and fetal presentation at the time of delivery, cesarean delivery was associated with a decreased risk for death in the delivery room or within 24 hours after delivery(35)

In Addis Ababa, Ethiopia, using Three public hospitals with neonatal intensive care units were selected based on their number of preterm admissions. Medical records of preterm neonates were collected from the registry log book of the unit. Retrospective data were collected from the five-year admissions of preterm births to the unit. The mean age of the mothers was 26 years, with 51.7% being above the mean age and 48.3% younger than 25 years. The most common mode of delivery was spontaneous vaginal delivery, followed by cesarean section and instrumental delivery. 156 mothers had been diagnosed with at least one medical problem during their pregnancy,51% of preterm births were male.(36)

In Ethiopia A total of 30 studies were included in this systematic review and meta-analysis. The overall pooled prevalence of preterm birth in Ethiopia was 11.4%. preterm birth was associated with pregnancy induced hypertension, premature rupture of membrane, rural residence, the mother having multiple pregnancies, and anemia during pregnancy.

2.9. Conceptual Framework

After reviewing different literatures about outcome of preterm neonate with apnea treat aminophylline and factors associated the following conceptual frame work is adapted and showing the interaction between socio-demographic, and neonatal clinical condition, and association between dependent and independent variables.

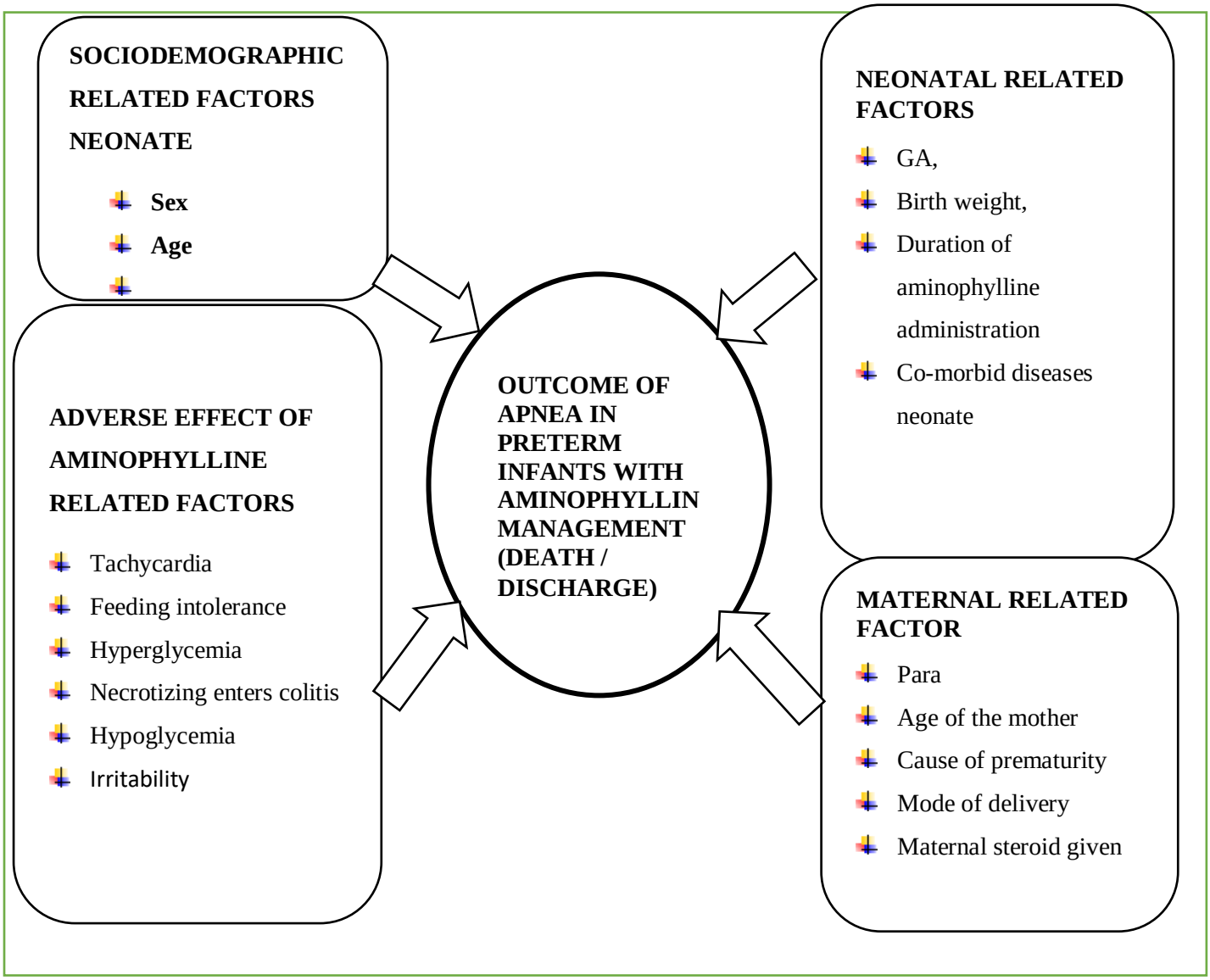

Figure 1:Conceptual frame work of factors that could affect the outcome of preterm neonate with apnea treated using aminophylline, among neonates admitted to NICU in Addis Ababa Public Hospitals, Ethiopia, 2024.(12,18,19,26)

3. OBJECTIVES

3.1. General objective

- To determine outcome of Apnea Management with Aminophylline and associated factors among preterm infants admitted to public hospitals, Addis Ababa, Ethiopia 2024.

3.2. Specific Objective

- To determine outcome of Apnea Management with in preterm neonate admitted at public hospital, Addis Ababa, Ethiopia, in 2024.
- To identify factors associated with outcome of apnea of prematurity treated using aminophylline in preterm neonate admitted at public hospital of Addis Ababa, Ethiopia, in 2024.

4. Methods and Materials

4.1. Study Area and Period

4.1.1. Study Area

The study was conducted at public hospitals of Addis Ababa, the capital city of Ethiopia and seat of charter of African union. Addis Ababa has eleven sub-cities and according to the central statistics agency population projection of the city in 2023 is estimated to be 5.5 million. In Addis Ababa there are 12 hospitals (six of them governed under federal government, six of them governed under Addis Ababa city health bureau, one owned by police force and one owned by defense army). Among all government hospitals available in the city currently, eleven of them have neonatal intensive care unit (NICU) service. Therefore, this study was done conducted in four randomly selected public hospitals of Addis Ababa which have NICU service. The four randomly selected hospitals are Tikur Anbessa Specialized Hospital (TASH), St' Paul's Hospital Millennium Medical College (SPHMMC), Gandhi Memorial Hospital (GMH) and St' Peter Specialized Hospital (SPH).

Tikur Anbessa Specialized Hospital (TASH)**:** was established in 1966 and located in Lideta Sub City. It has 543 beds and patients are admitted in different specialty and sub-specialty unit. Among these units NICU is one and in average about 2000 neonate admitted annually, of which about 34% are preterm neonates.

St' Paul's Hospital Millennium Medical College (SPHMMC) is one of the governmental hospitals in central Addis Ababa, Addis Kifle Ketema. It has different disciplines in both inpatient and outpatient service. In its NICU annually about 2500 newborns admitted in average according to the data from health management information system (HMIS) registration. Of total admission about 37% of them are preterm neonates.

Gandhi Memorial Hospital (GMH) is one of those governed by Addis Ababa city administration health bureau and specializes in maternity services. The hospital was established in 1951 E.C. According to HMIS data about 2000 newborns were admitted in NICU, of which about 39% are preterm neonates.

St' Peter Hospital (SPH) is one of the governmental hospitals in Addis Ababa. It has different service disciplines unit. Among these units NICU is one and annually about 1800 newborns admitted in average, of which about 36% of them are preterm neonates.

4.1.2. Study Period

Data on neonates with apnea of prematurity who were admitted from January 1, 2021, to December 31, 2023, were collected. Data collection was conducted from February 19 to March 19, 2024.

4.2. Study Design

A facility-based cross-sectional study design was employed for this study.

4.3. Population:

4.3.1. source population

Medical charts of preterm neonates with apnea of prematurity who took aminophylline, and admitted to neonatal intensive care units (NICU) of public hospitals in Addis Ababa, Ethiopia

4.3.2. Study population:

Medical charts of selected preterm neonates with apnea of prematurity (AOP) admitted to NICU of public hospitals in Addis Ababa, Ethiopia and treated with aminophylline from Jan 1, 2021- Dec 31, 2023.

4.4. Eligibility Criteria

4.4.1. Inclusion Criteria

- This study included medical charts of preterm neonates who were admitted to NICU of Public Hospitals in Addis Ababa, had AOP, and received Aminophylline for management of the AOP during the study period

4.4.2. Exclusion Criteria

- Charts of preterm neonates that missed important information were not included in this study. Furthermore, the study did not include infants who were referred or for whom the administration of aminophylline medication was declined.

4.5.1. Sample Size Determination

The required number of participants was estimated using the single population proportion formula with a 50% (p= 0.5) population proportion at 95% confidence level and 5% (0.05) margin of error (D). Hence, the required sample size is:

$$n = \frac{\left(z_{\alpha/2}\right)^2 p(1-p)}{d^2} = \frac{(1.96)^2 0.5(1-0.5)}{0.05^2} = 384$$

Where;

- n = the minimum sample size required
- p= estimated proportion (50%) = 0.5

- z = the standardized value for the confidence level 95% (or alpha=0.05) which is 1.96
- d = the margin of error between the sample and the population (0.05).

10% Contingency

By adding 10 % Contingency the final calculated sample size was n = 384+38 = **422**

4.5.2. Sampling Procedure

Samples were recruited using systematic random sampling technique. The sample size was allocated proportionally to the four randomly selected hospitals based on the average number of preterm neonates with apnea of prematurity treated with aminophylline and admitted to NICU each year. According to HMIS report of the four hospitals; The annual average number of preterm neonate admission to NICU in TASH, SPHMM, GMH, SPH is 672, 972, 780, and 648, respectively. After allocating proportionally, the sample required from TASH, SPHMMC, GMH, and SPH was 93,107,133, and 89, correspondingly. The total number of preterm neonates with apnea who took aminophylline in the study period are 9216. So, K=9216/422=22. As a result, to achieve required sample size, every 22th admitted preterm neonate was selected for the study. The first chart (starting point) was selected by randomly choosing from the numbers 1 to 22.

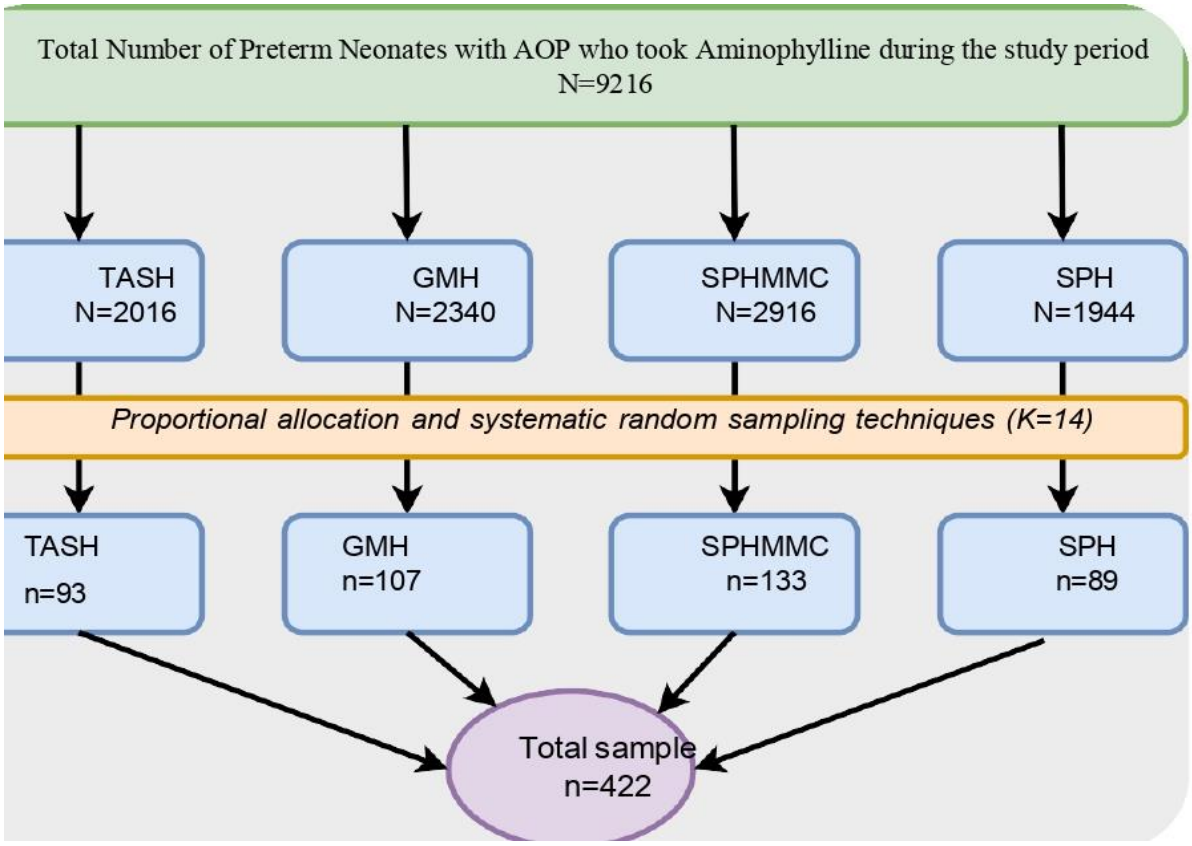

Figure 2: diagram of sampling procedure for the study on the outcome of Apnea Management with Aminophylline and associated factors among preterm infants admitted to public hospitals, Addis Ababa, Ethiopia.

4.6. Study variables

4.6.1. Dependent Variables

- Outcome of apnea management with Aminophylline: died or discharged

4.6.2. Independent Variables

- **Maternal factors:** Cause of prematurity, Mode of deliver**,** maternal Age, use of steroid ANC follow up.
- **Neonatal factors:** Age of the neonate in days, sex of the neonate, gestational age at birth, Birth weight, duration of aminophylline administration morbid disease of neonate
- **Aminophylline adverse effect related factors:** Tachycardia, feeding intolerance, Hyperglycaemia, Necrotizing enter colitis**,** hypoglycaemia and irritability.

4.7. Operational Definition

Neonate: -New born from 0 to 28 days of age(37)

Preterm Birth: -Babies born alive before 37 weeks of completed pregnancy(37)

Late preterm birth: babies born alive before 37 weeks of completed pregnancy (37)

Early preterm birth: -babies born alive before 34 weeks of completed pregnancy (37)

Gestational age: is a measure of the age of a pregnancy which is taken from the woman's last menstrual period (LMP) or early ultra sound assessment(37)

Birth weight: is the first weight of the fetus or newborn obtained after birth(37)

4.8. Data Collection Tool and Procedure

Data collection tool was developed and adapted by reviewing relevant literatures (12,19,26,38). A checklist was used to extract data by reviewing the NICU admission register and patient chart. The checklist is prepared in English. The checklist had three parts. The first part of the checklist was aimed to extract sociodemographic data. The second part focused on neonatal and maternal factors. The last part of the checklist tried to obtain data related to aminophylline treatment and its adverse effects. Based on the checklist, electronic-based data collection was conducted using the Kobo Collect mobile application. The use of Kobo Collect was done to ensure data consistency, completeness, accuracy, and avoid errors. The data collection pace and trend were followed on a daily basis since data is automatically submitted to the Kobo server.

Data was collected by three trained BSc nurses.

4.9. Data Quality Assurance

The validity of the instrument was checked by a senior neonatologist. Before the actual data collection, a pretest was conducted on 25 (5% of the actual sample size) eligible preterm neonates at Zewditu Memorial Hospital.

The supervisor and data collectors were trained for one day about the aim of the study, the relevance of the study, the confidentiality of client information, eligibility criteria, and how to use Kobo Collect mobile application for data collection and submit finalized forms. Provision of training to data collectors and supervisor ensured to have valid data. The collected data was reviewed on a daily basis by the principal investigator, and appropriate feedback was given to the data collectors and supervisor.

4.10. Data Analysis

The collected data was imported to SPSS 27 for further data management and analysis. Categorical variables were described using frequency and percent. Continuous variables were described using a

relevant combination of measure of central tendency and measure of dispersion. Association between categorical variables and outcome was examined using chi-square test of association.

Logistic regression was fitted to identify factors significantly associated with outcome of apnea treatment using aminophylline. P-value <0.25 was used as a cutoff point to select variables eligible for multivariable logistic regression model. Results of logistic regression analysis is reported using odds ratio with its 95% confidence interval (CI) and p-value. Variables with p-value less than 0.05 were considered as significantly predictors of outcome of aminophylline treatment for preterm neonates with apnea of prematurity (AOP). Model fitness and multicollinearity were examined using Hosmer-Lemeshow test and Variance Inflation Factor (VIF), respectively.

4.11. Ethical Consideration

This research work was approved by Ethical Review Committee of school of nursing and midwifery, Addis Ababa University (AAU) before the start of data collection. Ethical clearance was obtained from research and ethics committee of school of nursing and midwifery, AAU. Official letter written was provided to each selected hospital. After getting permission from each hospital, data was collected by reviewing NICU admission register and patient chart. Name and MRN are removed from the collected data to maintain confidentiality and privacy. Data is kept in password protected personal computer.

5 RESULTS

From the 422 patient charts and registers reviewed, 415 of them were included in this study giving a response rate of 98.3%. The remaining 7 (1.7%) medical charts were excluded due to missing data. The finding of the data analysis is presented below under sociodemographic characteristics, outcome of apnea management and the associated factor subheadings.

5.1 Sociodemographic and obstetric characteristics

5.1.1 Sociodemographic

The majority of these neonates (74.0%) were admitted within the first hour of life, while 26.0% were admitted after the first hour. Regarding the sex distribution, 64.6% of the neonates were male, and 35.4% were female. The mean age of mothers were 24.8 years. The age distribution of the mothers showed that 55.7% were between 18-24 years old, and 44.3% were between 25-34 years old **(Table 1).**

5.1.2 Obstetric characteristics

Most pregnancies were singleton, accounting for 78.8% of the cases, followed by twins at 20.0%, and triplets at 1.2%. The causes of prematurity varied, with the most commonly known causes included pre-eclampsia (15.2%), premature rupture of membranes (PROM) (15.4%), and non-reassuring fetal heart rate patterns (NRBPP) (12.3%). A significant proportion of mothers (83.6%) had a previous history of preterm delivery, while 16.4% did not. In terms of parity, 64.1% of the mothers were primiparous, and 35.9% were multiparous**.** Regarding the mode of delivery, 43.4% of the deliveries were spontaneous vaginal deliveries (SVD), 55.4% were cesarean sections, and 1.2% were instrumental deliveries. The vast majority of deliveries (97.8%) took place in health institutions, with only 2.2% occurring at home. Maternal steroid administration was reported in 81.2% of the cases, while 18.8% did not receive steroids (**Table 1).**

Table 1: Sociodemographic and maternal characteristics among neonates who received aminophylline treatment for apnea of prematurity in selected four public hospitals, Addis Ababa, Ethiopia 2024 (N=415).

Characteristics	Category	Frequency	Percent
Age of neonate at admission	Less than one hour	307	74
	Greater than one hour	108	26
Sex of neonate	Male	268	64.6
	Female	147	35.4
Age of the mother	18-24	231	55.7
	25-34	184	44.3
Type of pregnancy	Singleton	327	78.8
	Twins	83	20
	Triplites	5	1.2
Cause of prematurity	Abruptio placenta	14	3.4
	Unknown	98	23.6
	Breech presentation	10	2.4
	Triplets	5	1.2
	PIH	5	1.2
	CHTN	18	4.3
	APH	17	4.1
	Eclampsia	15	3.6
	NRBPP	51	12.3
	Oligohydramnios	7	1.7
	Placenta previa	8	1.9
	Pre-eclampsia	63	15.2
	Twin	40	9.6
	PROM	64	15.4
Previous history of preterm delivery	Yes	347	83.6
	No	68	16.4
Parity	Primiparous	266	64.1
	Multiparous	149	35.9
Mode of delivery	SVD	180	43.4
	Caesarean Section	230	55.4
	Instrumental Delivery	5	1.2
Place of delivery	Home delivery	9	2.2
	Health Institution	406	97.8
Maternal steroid given	Yes	337	81.2
	No	78	18.8

5.2 Birthweight, gestational age, and neonatal complications

Regarding birthweight, 8.9%, 64.1%, and 27.0% of neonates were below 1 kg, 1 to 1.5 kg, and 1.5 to 2.5 kg, respectively. Very preterm, moderate preterm, and late preterm infants accounted for 34.9%, 50.8%, and 14.2% of the study participants, respectively. The most common complications found were hypothermia (68.7%) and sepsis (56.1%). There were 6.5% premature neonates. About 12.5% of

premature neonates presented with pulmonary hemorrhage. There were ten premature neonates diagnosed with meconium aspiration and five of them didn't survive **(Table 2).**

Table 2: Birthweight, gestational age, and neonatal complications among premature neonates admitted to the selected four public hospitals, Addis Ababa, Ethiopia 2024 (N=415).

Characters	Category	Frequency	Percent
Birth Weight (Kg)	1.5 kg to 2.5 kg	112	27
	1Kg to 1.5 kg	266	64.1
	Below 1 kg	37	8.9
Gestational age	≥28 & <32 weeks	145	34.9
	≥32 & <34 weeks	211	50.8
	≥34 & <37 weeks	59	14.2
Sepsis	No	182	43.9
	Yes	233	56.1
Asphyxia	No	388	93.5
	Yes	27	6.5
Pulmonary hemorrhage	No	363	87.5
	Yes	52	12.5
Meconium aspiration	No	405	97.6
	Yes	10	2.4
Hypothermia	No	130	31.3
	Yes	285	68.7

5.3 Management of apnea of prematurity

Most neonates (74.0%) started aminophylline on the first day, with nearly equal distribution between maintenance (49.4%) and loading doses (50.6%). Half of the neonates (49.2%) began treatment within 11 hours of birth. Post-treatment, apneic episodes occurred in 42.7% of the cases. Additional treatments included nasal oxygen (70.8%), CPAP (99.2%), and mechanical ventilation (10.1%). Adverse effects included tachycardia (57.1%), feeding intolerance (68.2%), and hypoglycemia (46.3%). An IV line was required for 83.6% of cases. Treatment duration was less than 10 days for 61.2% of neonates **(Table 3)**.

Table 3: Aminophylline administration and its adverse effects related characteristics of neonates who received aminophylline treatment for apnea of prematurity in selected four public hospitals, Addis Ababa, Ethiopia 2024 (N=415).

Characters	Category	Frequency	Percent
Age of initiation of aminophylline	1 days	307	74
	2 days	95	22.9
	3 days	13	3.1
Dose of aminophylline	Maintenance Dose	205	49.4
	Loading Dose	210	50.6
Time of initiation of aminophylline with hour	< 11 hours	204	49.2
	>11 hours	211	50.8
Apneic episodes after aminophylline initiation	No	237	57.1
	Yes	178	42.8
Additional treatment	Nasal O2	294	70.8
	CPAP	412	99.3
	Mechanical ventilation	42	10.1
	KMC	114	27.5
Any adverse effect detected while on aminophylline	Tachycardia	237	57.1
	Feeding intolerance	283	68.2
	Hyperglycemia	55	13.3
	Necrotizing enterocolitis	22	5.3
	Hypoglycemia	192	46.3
	Irritability	278	67
Any time IV line is required for administering aminophylline	No	68(16.4)	68
	Yes	347(83.6)	347
Duration of aminophylline treatment	Less than 10 days	256(61.2)	256
	Greater than or equal to 10 days	159(38.8)	159

5.4 Outcome of apnea of prematurity

The pie chart below shows the outcome for 415 premature neonates who received aminophylline treatment for Apnea of Prematurity (AOP): 67.71% of them improved, and 32.29% died.

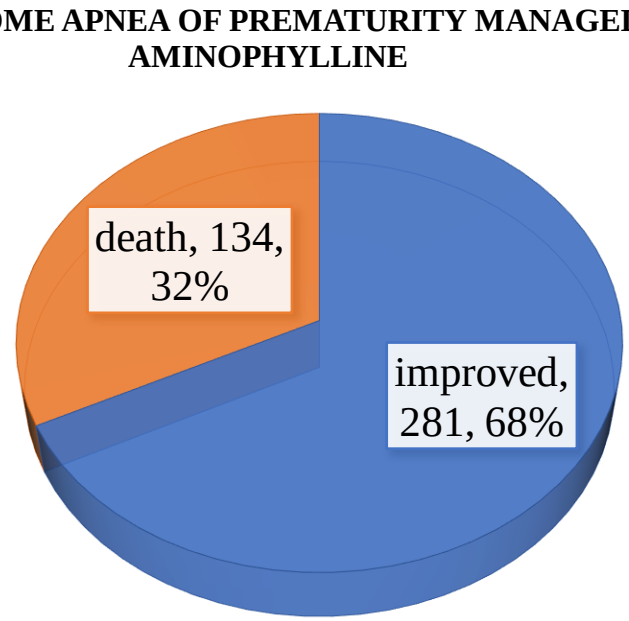

Figure 3: a pie chart about outcome of neonates who received aminophylline treatment for apnea of prematurity in selected four public hospitals, Addis Ababa, Ethiopia 2024.

5.5 Predictors of the Outcome of Aminophylline-Managed Apnea of Prematurity

Using backward stepwise variable selection approach, a multivariable logistic regression was fitted to identify variables significantly associated with outcome of aminophylline-managed apnea of prematurity. Accordingly, six variables (birthweight, presence of pulmonary hemorrhage, occurrence of apnea episode after initiation of aminophylline, use of nasal oxygen, presence of hypoglycemia, and duration of aminophylline treatment) were identified as significant predictors.

Neonates with a birthweight of less than 1 kg had 18.9 times higher odds of death compared to those with a birthweight of 1.5 kg or more. Neonates with a birthweight between 1 kg and 1.5 kg also had 2.8 times higher odds of death compared to those with a birthweight of 1.5 kg or more. Neonates with pulmonary hemorrhage had 3.7 times higher odds of death compared to those without pulmonary hemorrhage. Premature neonates who had an apnea episode after initiation of aminophylline had 2.5 times higher odds of death compared to those who did not. Neonates who did not receive nasal oxygen had 53.1 times higher chance of death compared to those who did. Neonates with hypoglycemia had 3.3 times higher likelihood of death compared to those who didn't experience hypoglycemia. Mortality was higher among premature neonates who stopped aminophylline in less than 10 days (39.1%) compared to those who stopped after 10 days (21.4%). Premature neonates who were treated with aminophylline for less than 10 days had 4.8 times higher odds of death compared to those treated for 10 days or more **(*Table 4*).**

Table 4: A multivariable binary logistic regression analysis of predictors of the Outcome of Aminophylline-Managed Apnea of Prematurity among neonates admitted in selected four public hospitals, Addis Ababa, Ethiopia 2024 (A multivariable logistic regress.

Predictor	Improved	Death	AOR [95% CI]	p-value
Birthweight				
<1 kg	97 (86.6)	15 (13.4)	18.9 [4.6, 77.9]	<0.001
1 kg to 1.5 kg	177 (66.5)	89 (33.5)	2.8 [1.1, 7.1]	0.029
≥1.5 kg	7 (18.9)	30 (81.1)	1	
Pulmonary hemorrhage				
Yes	15 (28.8)	37 (71.2)	3.7 [1.2, 11.1]	0.019
No	266 (73.3)	97 (26.7)	1	
Apnea episode after initiation of aminophylline				
Yes	81(45.8)	96(54.2)	2.5 [1.2, 5.1]	0.011
No	199(84.0)	38(16.0)	1	
Received nasal oxygen				
Yes	267(90.8)	27(9.2)	1	
No	14(11.6)	107(88.4)	53.1 [24.0, 117.3]	<0.001
Hypoglycaemia				
Yes	111(57.8)	81(42.2)	3.3 [1.5, 7.4]	0.003
No	170(76.2)	53(23.8)	1	
Duration of aminophylline treatment				
<10 days	156(60.9)	100(39.1)	4.8 [2.0, 11.4]	<0.001
≥10 days	125(78.6)	34(21.4)	1	
A Hosmer-Lemeshow test with 415 observations and 10 groups yielded a chi-square statistic of 7.51 (p = 0.4823), indicating an acceptable model fit. There was no multicollinearity issue (maximum VIF=1.38). The model has an excellent accuracy in predicting outcome of Aminophylline-Managed Apnea of prematurity (Area under the ROC curve (AUC)=0.944				

6. DISCUSSION

Aim of the study was to assess the outcome of aminophylline treatment for apnea of prematurity and identify its associated factors. In this study, one-third of children treated with aminophylline for apnea of prematurity have died. In addition, factors significantly associated with bad prognosis (i.e. death) of aminophylline-managed apnea of prematurity were extremely or very low birthweight, presence of pulmonary hemorrhage, occurrence of apnea episode after aminophylline initiation, experiencing hypoglycemia, shorter duration of aminophylline treatment, and lack of nasal oxygen support.

This study found that mortality was higher in extremely low birthweight (ELBW) or very low birthweight (VLBW) neonates treated with aminophylline for apnea of prematurity. A study conducted in Botswana supports this finding. In the Botswana study, the odds of mortality were about six times higher in premature neonates with very low birth weight (39). Neonates with extremely low birth weight (ELBW) or very low birth weight (VLBW) are at risk for multiple organ dysfunction, immature immune systems, and potentially life-threatening infections. Consequently, they are at a higher risk of death (40).

This study has also found that provision of nasal oxygen support decreases incidence of death among aminophylline-managed apnea of prematurity. Likewise, a study has reported that Nasal O2 resulted in decreased incidence of apnea and death, as well as improved oxygenation (41). Nasal oxygen therapy delivers humidified and heated air blended with oxygen through a nasal cannula, providing a positive airway pressure. Consequently, decreased work of breathing, improved oxygenation, and reduced rates of intubation. Preterm neonates often have underdeveloped lungs and may fight to keep adequate oxygen levels without support. As a result, such neonates require oxygen therapy to achieve optimal oxygen saturation levels. The lack of such therapy could therefore rise the risk of respiratory distress and other serious complications, contributing to higher death rates (42).

In this study, pulmonary hemorrhage was significantly associated with a high mortality rate. This is in line with several studies. According to the study conducted in Botswana, pulmonary hemorrhage was found to increase neonatal mortality up to 34-fold (39). Another study also found that the co-presence of pulmonary hemorrhage and apnea of prematurity doubles the risk of mortality in premature neonates (43). Pulmonary hemorrhage prevents effective oxygen exchange, leading to hypoxia and death (44).

Again, in this study, mortality was higher among neonates who were affected by hypoglycemia. This finding is in line with a study done in Egypt(45) and USA(46). Hypoglycemia in preterm neonates can lead to significant neurological and developmental sequelae if left untreated. In addition, hypoglycemia

can impair the function of various organs, including the heart and brain, leading to life-threatening situations. Consequently, it increases the risk of mortality (47).

In this study, mortality was higher in preterm neonates who received aminophylline for a relatively shorter period of time. This is consistent with existing evidence. Aminophylline treatment duration is crucial for neonates' respiratory system maturation, reducing the risk of complications like respiratory distress syndrome and bronchopulmonary dysplasia. Longer durations improve apnea management and survival outcomes (48,49).

7 CONCLUSIONS

The findings of this study revealed that one-third of neonates treated with aminophylline for apnea of prematurity died. Mortality was notably higher in neonates with extremely or very low birthweight, likely due to their increased vulnerability to infections and multiple organ dysfunction. The provision of nasal oxygen support was found to significantly reduce mortality, highlighting its importance in managing apnea of prematurity. Pulmonary hemorrhage was another critical factor associated with high mortality, as it leads to severe respiratory distress and hypoxia. Additionally, hypoglycemia was linked to increased mortality. The duration of aminophylline treatment also played a crucial role.

7.1. Strength of the study

This study has tried to identify independent predictors (using a multivariable analysis) by controlling for confounding effect.

7.2. Limitation of the study

The study was limited to merely on secondary data. So, analysis of associated factors for treatment outcome of apnea was based on only information that could be obtained from charts. In addition, it didn't include information's related to families' economic status, educational level, and occupation. The other lost to follow up and refer to other institution were not included. On the other hand, diagnosis of apnea was based on the diagnosis obtained from the charts that might be misdiagnosed.

8. RECOMMENDATIONS

Based on the finding of study, the following recommendation could be mentioned: -

For Health Professionals:

- Health professionals should give great emphasis to premature neonates with pulmonary hemorrhage
- Health professionals should optimize the dose and duration of aminophylline treatment
- Premature neonates with hypoglycaemia are at higher risk of death. So early detection of hypoglycaemia and immediate treatment should be considered.

For Hospital Directors:

- Hospitals should ensure that all neonates who require nasal oxygen therapy have access to this life-saving intervention.

For Health Bureaus:

- Health bureaus should develop policies that support the implementation of enhanced care protocols for extremely/very low birthweight neonates and the universal provision of nasal oxygen therapy.
- Health bureaus should allocate funding for further research into the management of pulmonary hemorrhage, the optimal duration of aminophylline treatment, and strategies for preventing hypoglycemia.

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10 ANNEXES

Annex I**: Information Sheet**

Addis Ababa University College of Health Sciences, school of Nursing and Midwifery Graduate study program. Here, at Addis Ababa University College of Health Sciences, School of nursing and midwifery graduate Study Program, currently I will be undertaking research on a topic entitled Outcome of Apnea Management with Aminophylline and associated factors among preterm infants admitted to public hospitals, Addis Ababa, the aim of this form is to make the concerned body clear about the purpose of the research, data collection procedure and get permission to conduct the research.

The objective of the study: Outcome of Apnea Management with Aminophylline and associated factors among preterm infants admitted to public hospitals, Addis Ababa, Ethiopia.

Design of the study: institution based, cross-sectional design.

Risks and benefits: The result of the study helps programmers or policy makers to design intervention related to treatment of apnea. In this way you may get benefit from the intervention policy. There is no payment and risk or discomfort as a result of Participating in this study except that you lost your time.

Confidentiality; All information given by you will be kept strictly confidential. Any of your personal information will not register. The information obtained in this study will be used only for research purposes.

Address of the principal investigator:

Name –Abenezer Admasu

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Supervisor: Name_____ Signature: _____

Date: _____

Phone- +251935285817

Annex II checklist

Part 1: Sociodemographic neonate

S. N	characters	options
101	Age(hrs.)	_____
102	Sex	☐ Male ☐ Female

Part 2 neonatal factor of prematurity of apnea

S, N	characters	options
201	Birth Weight(gm)	_____
202	Gestational age	☐ 28—32 weeks ☐ 32-34 weeks ☐34-37 weeks
203	Co morbid of neonatal factor chose more than one possible	☐Sepsis ☐Asphyxia ☐Pulmonary Hemorrhage ☐ Meconium Aspiration ☐Hypothermia

PART 3: maternal Factors for Prematurity apnea

S.N	Characters	Options
301	Type of pregnancy	☐ Singleton ☐ Twins ☐ Triplites
302	Cause of prematurity	
303	Previous history of preterm delivery	☐Yes ☐No
304	Parity	
305	Mode of delivery	☐. SVD ☐ Cesarean Section ☐. Instrumental Vaginal Delivery
306	Place of delivery	☐ Home delivery ☐Health Institution
307	Maternal steroid given	☐ Yes ☐ No
308	Age of the mother	

Part 4: outcome using of aminophylline and related factor

S. N	Characters	Options
401	Reason of Aminophylline administration	☐. Prophylaxis ☐ Therapeutic
402	Age of initiation of aminophylline	
403	Dose of aminophylline	☐. Loading Dose ☐ Maintenance Dose
404	Time of initiation of aminophylline with hour	
405	Number of apneic episodes after aminophylline initiation	
406	Additional treatment approach of apnea	☐ Nasal O2 ☐ CPAP ☐ Mechanical ventilation ☐ KMC ☐ Other
407	Any adverse effect detected while on aminophylline (Multiple answer is possible)	☐Tachycardia ☐Feeding intolerance ☐Hyperglycemia ☐Necrotizing enterocolitis ☐Hypoglycemia ☐lrritability

408	Any time IV line is required only for administering aminophylline	☐Yes ☐ No
409	Duration of aminophylline treatment	
410	Outcome apnea withing aminophylline	☐ Improved ☐ Died

Declaration

This thesis by **ABENEZER ADMASU**, I declare that this is an original thesis has been written by me and has not been submitted for any previous degree. This thesis is accepted in its present form by the Advisors and Board of examiners as satisfying thesis Thesis requirement for the Degree of Master of Science in Neonatal Nursing.

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