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Very early complications of neonatal asphyxia

Abstract

Background: Neonatal asphyxia may develop complications and may lead to death. This study aimed to know the incidence of complications of neonatal asphyxia within 24 hours after birth.

Methods: This cohort study was performed from June 2015 to May 2016. The inclusion criteria were gestational age ≥28 weeks or birth weight ≥1000 grams and need positive pressure ventilation (with or without intubation) for 30 seconds or more. Neonates with major congenital anomalies and early-onset infection were excluded from the study. Subjects were followed up for 24 hours to identify any complications related to neonatal asphyxia. Further follow-up was done until the subject was discharged home or died during hospitalization. Complications of neonatal asphyxia monitored were central nervous system, cardiovascular system, respiratory system, gastrointestinal tract system, urinary tract system, hematology system, metabolic disorder, and electrolyte imbalance. An attending neonatologist or neonatology trainee performed a clinical assessment of complications, and a trained medical doctor did the data collection. We analyzed the incidence of neonatal asphyxia complication, mortality, and gestational age sub-analysis. A student t-test with a 95% significance level was used to analyze dichotomous data and regression analysis for correlation between the level of resuscitation and the number of complications.

Results: There were 94 subjects included in the study. There was no significant difference in complications in sex, birth weight, gestational age, 1 and 5-minute Apgar score, and level of resuscitation. Seventeen (18.1%) of subjects had no complications. The incidence of complications was respiratory system 67%, hypoglycemia 37.2%, electrolyte imbalance 8.5%, CNS 6.4%, CVS and hematology system complications were 2.1%, and GIT 1.1%. Subjects with 1 organ complication were 48.9%, 2 complications, 3 complications and 4 complications were 24.5%, 7.4%, and 1.1% respectively. Lower gestational age had more complications (p: 0.025). There was weak correlation between level of resuscitation and number of complication (r^2: 0.017, p: 0.22), for term (r^2: 0.31; p: 0.27), preterm (r^2: 0.31; p: 0.27), and very preterm (r^2: 0.00; p: 0.98). Three out of five death cases occurred within first week.

Conclusion: The most common neonatal asphyxia complication was respiratory distress which may lead to early neonatal death.

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Background

Neonatal asphyxia is one of the three leading causes of death globally, especially in developing countries, where about 700,000 neonates die each year because of neonatal asphyxia in developing countries.[1] One-third of neonatal deaths occur in the first 24 hours and 75% in the first week. (World Health Organization, 2020) In Indonesia, neonatal asphyxia is the second cause of neonatal death. Its contribution was 21% to all neonatal death, or an absolute death estimation of 13,000 neonates per year.[2] (Soleman, 2020) Our hospital data showed that 13.2% of neonatal death caused by neonatal asphyxia; this occurred mainly in the early neonatal period (91.4%). Its contribution to early neonatal death was 20.9%. Within the last decade, neonatal mortality in Indonesia was decreased, from 20/1000 live birth in 2003 to 19/1000 live birth in 2012, and 12.4 (2019). (Institute for Health Metrics and Evaluation (IHME), 2020) Neonatal asphyxia as a second leading cause of death after complications of prematurity decreased from 25% to 21%. This death mainly occurred in a health facility with limited resources.[2,3] To reduce the neonatal mortality rate in Indonesia needs improvement in the management of neonatal asphyxia.[2]

The basic pathophysiology of neonatal asphyxia is hypoxia, which occurs in all organs/systems. The hypoxia may lead to complications in the organs. The complications may occur immediately or later. It has long been known that asphyxia may lead to complications in organs or systems soon after birth, such as the central nervous system, cardiovascular system, respiratory system, gastrointestinal system, and renal systems. Some of these infants who got complications died.[4,5] The complication of neonatal asphyxia in publications mainly only stated organs involved, not specific in time after birth. Some publications said complications within days or weeks after birth.[6-11] it is essential to know the complication of asphyxia that occurs soon after birth because it may lead to early neonatal death. Appropriate management of the complication prevents death from neonatal asphyxia. This study aimed to know the incidence of complications of neonatal asphyxia within 24 hours after birth.

Methods

This study was performed from June 2015 to May 2016 in the neonatal ward, Maternal-Perinatal Installation, Sardjito General Hospital (SGH)/Neonatology Division, Department of Child Health, Universitas Gadjah Mada, as part of the Lactate Project. SGH is a tertiary teaching hospital, located in Yogyakarta Special Region, Indonesia. The capacity of the neonatal ward is 20 beds in NICU and 40 beds for high-risk neonates. The annual admission is about 1,300 neonates, with about 1/3 being referral cases. We included all live birth inborn with gestational age ≥28 weeks or birth weight ≥1000 grams, and need positive pressure ventilation (with or without intubation) at least 30 seconds into the study. Neonates with major congenital anomalies, and early-onset infection (sepsis and pneumonia), were excluded from the study. The early-onset neonatal sepsis was defined

as clinically or proven positive blood culture or needed antibiotics starting within 48 hours after birth. The diagnosis of pneumonia was based on chest radiography consistent with pneumonia.

The subjects included in the study were followed up for 24 hours and monitored whether there was any complication related to neonatal asphyxia. Neonatal asphyxia was defined as newborn needed positive pressure ventilation for at least 30 seconds, with or without intubation. The procedure of neonatal resuscitation was based on American Heart Association Guidelines.[12] Further follow-up was done until the subject was discharged home or died during hospitalization. Complications of neonatal asphyxia monitored were central nervous system (CNS), cardiovascular system (CVS), respiratory system, gastrointestinal tract system (GIT), urinary tract system, metabolic disorder, electrolyte imbalance, and hematology system.

The complication of CNS was defined as hypoxic-ischemic encephalopathy (HIE) based on Sarnat and Sarnat classification[13] or any seizure. CVS complication if there was any low perfusion, hypotension/shock, or need inotropic. Low perfusion was determined by clinical examination, and the capillary refill time >3 seconds. Hypotension/shock was defined as blood pressure <5 percentile below the normal range for certain birth weight and postnatal age.[14] Inotropic needed was dopamine and/or dobutamine. Respiratory system complication identified if there was any sign of respiratory distress, apnea, need for oxygen supplementation, or respiratory support (continuous positive airway pressure or mechanical ventilator). Score Downes[15,16] was used to assess respiratory distress, and respiratory distress defined if the scored was ≥4. Apnea if there were no breathing ≥20 seconds or <20 seconds with bradycardia. Oxygen supplementation was defined if the subject needed nasal oxygen >21%. Respiratory support by mechanical ventilation was either with intubation or without intubation (nasal intermittent mandatory ventilation). GIT system complication if there was any sign or symptom of bloody gastric residual, abdominal distention or tenderness, vomiting, or feeding intolerance. The complication of the urinary tract system was anuria or no production of urine within the first 24 hours after birth. Metabolic system complication was identified as venous blood glucose <45 mg/dL, drawn within the first 1 hour after birth. Electrolyte imbalance was defined as an imbalance of sodium, potassium, or calcium. Hematologic system complication was defined as thrombocytopenia (platelet <150,000/mL) or any bleeding without any trauma. Clinical assessment of complications was performed by an attending neonatologist or neonatology trainee. Any neonatal death was audited by a neonatologist to determine the cause of death. We developed a data collection form, and a medical doctor was trained to fill the form. Incidence of neonatal asphyxia complication, mortality, and gestational age sub-analysis was done. Dichotomous data were analyzed by chi-square and continuous data by student t-test, with a 95% level of significance. Regression was used to analyze the correlation between the level of resuscitation and the number of complications. This study was approved by the Ethics Committee, Faculty of Medicine, Universitas Gadjah Mada, reference number KE/FK/1158/EC/2015.

Result

There were 173 subjects during the study period. Seventy-nine subjects were excluded because of congenital anomaly (6 cases), early-onset sepsis (70 cases), and congenital anomaly and early-onset neonatal sepsis (3 cases). The remaining 94 subjects were analyzed. There was more male in the study of our subject, and mostly LBW or preterm. The 1-minute Apgar score of 4-6 was 70.2%, and 7-10 in 5 minutes was 66%. Most subjects (92.6%) need PPV only. Subject with VTP only consisted of 1 cycles (30 seconds) only were 50 (57.5%) subjects, followed by 2 cycles 32 (36.8%) subjects, and 3 cycles 5 (5.7%) subjects. There was no significant difference in sex, birth weight, gestational age, and 1-minute and 5-minute resuscitation level. Complications that occurred were not significantly different in sex, birth weight, gestational age, 1 minute and 5 minute Apgar score, and resuscitation level (Table 1).

Tabel 1 Characteristic of subjects

Variable	N (%)	Complication (N, %)		p
Sex		Yes	No	
- male	50 (53.2)	42 (84)	8 (16)	0.58
- female	44 (46.8)	35 (79.5)	9 (20.5)	
Birth weight				
- VLBW	22 (23.4)	19 (86.4)	3 (13.6)	0.89
- LBW	39 (41.5)	31 (79.5)	8 (20.5)	
- NBW	32 (34.0)	26 (81.2)	6 (18.8)	
- Large baby	1 (1.1)	1 (100)	0 (0)	
Gestational age				
- Very preterm	11 (11.7)	9 (81.8)	2 (18.2)	0.12
- Preterm	42 (44.7)	38 (90.5)	4 (9.5)	
- Term	41 (43.6)	30 (73.2)	11 (26.8)	
Apgar score 1 minute				
-3	28 (29.8)	25 (89.3)	3 (10.7)	0.23
-10	66 (70.2)	52 (78.8)	14 (21.2)	
-17	0 (0)	0 (0)	0 (0)	
Apgar score 5 minute				
-3	2 (2.1)	2 (100)	0 (0)	0.98
-10	30 (31.9)	28 (93.3)	2 (6.7)	
-17	62 (66)	47 (75.8)	15 (24.2)	
Resuscitation level				
- PPV only	87 (92.6)	70 (80.5)	17 (19.5)	0.43
- PPV + intubation	5 (5.3)	5 (100)	0 (0)	
- PPV + CC + drugs	2 (2.1)	2 (100)	0 (0)	

*CC, chest compression

We found that 17 (18.1%) of subjects had no complications. The most common complication was the respiratory system in 63 subjects (67%), followed by hypoglycemia in 35 subjects (37.2%), electrolyte imbalance in 8 subjects (8.5%), and CNS in 6 subjects (6.4%). CVS and hematology system complications were 2.1%, respectively, and only 1 (1.1%) subject had GIT complications. There was no urinary tract system complication. Almost half (48.9%) of subjects had 1 organ complication, followed by 46 (24.5%) subjects who had 2 complications, and 3 complications 7 (7.4%) subjects and 1 (1.1%) of the subject had 4 complications (Table 2).

According to gestational age, there were a significantly different in the number of complications (p: 0.025), the lower gestational age, the higher number of complications. There was weak correlation between level of resuscitation and number of complication (r^2: 0.017, p: 0.22; b1: 0.31). Sub-analyzes according to gestational age, we found weak correlation for term (r^2: 0.31; p: 0.27; b1: 0.37) and preterm subject (r^2: 0.31; p: 0.27; b1: 0.63) as well. In very preterm group, there was no correlation between level of resuscitation and number of complication (r^2: 0.00; p: 0.98; b1: 0.02) (Table 3). Five (5.3%) subjects died, consist 3 (60%) subjects died on days 2-4 after birth or early neonatal death, and 2 (40%) late neonatal death. All early neonatal death were very preterm (83.3%), and had more than 1 complication. The cause of death in all early neonatal mortality was severe respiratory distress.

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Table 2 Number of complications

Systems	Number of complications (n, %)					
	0	1	2	3	4	Total
	17 (18.1)	46 (48.9)	23 (24.5)	7 (7.4)	1 (1.1)	94 (100)
Respiratory	0	34	21	7	1	63
Hypoglycemia	0	10	18	6	1	35
Electrolyte	0	0	3	4	1	8
CNS	0	2	1	3	0	6
CVS	0	0	1	1	0	2
Hematology	0	0	1	0	1	2
GIT	0	0	1	0	0	1
Urinary tract	0	0	0	0	0	0

Table 3 Complications according to gestational age

Gestational age	Number of complications (n, %)				
	0	1	2	3	4
Very preterm	2 (18.2)	4 (36.4)	2 (18.2)	2 (18.2)	1 (9.1)
Preterm	4 (9.5)	20 (47.6)	15 (35.7)	3 (7.1)	0 (0)
Term	11 (26.8)	22 (53.7)	6 (14.6)	2 (4.9)	0 (0)

Discussion

The definition of neonatal asphyxia used in this study was the need for at least 30 seconds of positive pressure ventilation. This definition may not be appropriate, but it is practical in developing countries, where facilities and health personnel are limited; and different from previous studies.[6,17,18] In limited resources health facilities setting, it is not feasible to perform umbilical blood gas or other laboratory examination to support the diagnosis of neonatal asphyxia. In our study, the incidence of neonatal asphyxia complications that occurred within 24 hours in our study was 81.9%. Our result was higher than Goodwin et al. study. They found that morbidity after severe umbilical acidemia was 40.5%.[6] Our finding was lower than 85% of that found by Low et al.,[8] Also lower than Martin-Ancel's finding, where they found 82% of complications.[4] This result may be caused by a different definition of asphyxia and gestational age. In these three studies, umbilical vein blood gas was used to define asphyxia; and the time of complications was not stated in the first 24 hours. In our study, the subjects of preterm infants were more than 50%.

In our study, the most common complication of neonatal asphyxia was in the respiratory system (67%), followed by hypoglycemia (37.2%). The other complications were less than 10% and none in renal complications. van den Berg found the most frequent complications in umbilical artery pH <7.00 was the pulmonary problem (31%), followed by neurologic (23%), GIT (17%), cardiovascular 15%, and renal 5%.[9] In a case-control study, Sehdev also found that the most common complication in umbilical artery pH <7.00 was respiratory distress.[10] Our finding was different from the Valenzuela study. In this study, brain and renal dysfunctions were about 50%, hypocalcemia was at 44%, and severe respiratory distress and myocardial failure were at 24%.[6,19] found that cerebral dysfunction was the most common complication of neonatal asphyxia (31%), followed by respiratory distress, renal dysfunction, and cardiac dysfunction.[6] In another study, the most frequent organ involved was CNS (72%), followed by renal (42%), cardiac (29%), GIT (29%), and pulmonary (26%).[4] Acute kidney injury (AKI) is a common consequence of perinatal asphyxia, occurring in up to 56% of these infants.[20] In our study, there was no renal complication. In a case-control study on full-term infants by Low et al, 1994, asphyxia based on umbilical artery pH; showed that respiratory complications were 12%, CNS complications 8%, CV 8%, respiratory system 10%, kidney 0%; that not different between acidosis and not acidosis. In this study, complications were assessed 10 days after delivery.[8]

The difference in neonatal asphyxia complications is because of the different operational definitions of neonatal asphyxia and the definition of a complication. The major adaptation of the fetus to extrauterine life is the respiratory system. In neonates who suffer from asphyxia, this adaptation may not occur smoothly. So the manifestation is respiratory distress. In our study, the definition of respiratory complication was any sign of a respiratory problem. In a limited resources setting, it is crucial to detect early signs of a respiratory problem to allow appropriate management to prevent mortality. According to the number of complications, our finding that the subject had no complications was the same as the previous study,[4] but higher subjects with 1 complication, and lower with 2 complications. In this study was no subject with more than 2 complications.[4]

Overall neonatal mortality in our study subjects was 5 subjects (5.3%), consisting of 3 subjects (60%), was early neonatal death. There was no neonatal death in term and preterm subjects. In the very preterm group, our finding was higher than MacDonald et al. Their study found 52.9% death in the gestational group between 29-32 weeks,[21] but in preterm and term groups were lower. In this study, the definition of asphyxia was infants who required > 1-minute positive pressure ventilation.[21] Almeida et al.,[22] reported that the early neonatal mortality in asphyxiated neonates in 2010 was 0.65 per 1000 live birth. This study subjects were neonates born in health facilities around the country and had normal birth weight.[22] Our result of was higher than van den Berg's study.[9] They found mortality in umbilical artery <7.00 were 2 out of 84 (2.4%) compared to our result of 5/94 (5.3%). The overall survival in our study was higher than Padayachee et al.,[23] study (94.7% vs. 86.7%).[23] The definition of asphyxia in their study was Apgar score <6, and the subjects were >1800 grams.

It can be concluded that the most common neonatal asphyxia complication within 24 hours after birth was respiratory distress. This complication may lead to early neonatal death. Adequate management of this complication is mandatory to prevent death.

Conflicts of interest

The authors declared no potential conflict of interest.

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