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RESEARCH

Mortality in patients with hypoxic ischemic encephalopathy treated with therapeutic hypothermia

Terapötik hipotermi uygulanan hipoksik iskemik ensefalopatili hastalarda mortalite

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Abstract

Purpose: Hypoxic-ischemic encephalopathy is a heterogeneous clinical syndrome that occurs in the perinatal period and is characterized by altered consciousness or seizures, respiratory depression, and hypotension. The aim of this study was to evaluate mortality in hypoxic-ischemic encephalopathy patients receiving therapeutic hypothermia.

Materials and Methods: The study included 97 hypoxic-ischemic encephalopathy cases who underwent therapeutic hypothermia in the Neonatal Intensive Care Unit. The cases were evaluated for mortality and were divided into two groups: group 1 (n: 9, non-survivors) and group 2 (n: 88, survivors). Demographics, diagnoses, complications of hypoxic-ischemic encephalopathy, APGAR scores, blood support, and laboratory parameters were evaluated for mortality.

Results: The 97 hypoxic-ischemic encephalopathy cases in this study included 40 females and 57 males. There were 9 (9.3%) cases in group 1 (non-survivors) and 88 (90.7%) cases in group 2 (survivors). The most common etiology was umbilical cord prolapse 40 (41.2%), and the mortality rate in infants who developed hypoxic-ischemic encephalopathy due to meconium aspiration syndrome was found to be significantly high (29.4%). The risk of death was found to be increased 4.6-fold by the presence of hemorrhage in the infant, 7.3-fold by acute kidney injury, 15.5-fold by thrombocytopenia, 4.6-fold by administration of fresh frozen plasma, and 12.3-fold by pulmonary hemorrhage. A 1-unit increase in the number of intubated days was associated with a 1.2-fold increase in the risk of death.

Öz

Amaç: Hipoksik-iskemik ensefalopati perinatal dönemde ortaya çıkan ve bilinç bozukluğu veya nöbetler, solunum depresyonu ve hipotoni ile karakterize heterojen bir klinik sendromdur. Bu çalışmanın amacı terapötik hipotermi uygulanan hipoksik-iskemik ensefalopati hastalarında mortalite oranlarını değerlendirmektir.

Gereç ve Yöntem: Çalışmaya Yenidoğan Yoğun Bakım Ünitesinde terapötik hipotermi uygulanan 97 hipoksik-iskemik ensefalopati vakası dahil edildi. Olgular mortalite açısından değerlendirilmiş ve Grup 1 (n:9, hayatta kalmayanlar) ve Grup 2 (n: 88, hayatta kalanlar) olmak üzere iki grup oluşturulmuştur. Demografik veriler, tanılar, hipoksik-iskemik ensefalopati komplikasyonları, APGAR skorları, kan ürünü desteği ve laboratuvar parametreleri mortalite açısından değerlendirildi.

Bulgular: Bu çalışmaya 97 hipoksik-iskemik ensefalopati vakalarının 40'ı kadın ve 57'si erkek cinsiyet idi. Grup 1 (hayatta kalmayanlar) 9 (%9,3) ve Grup 2 (hayatta kalanlar) 88 olgu içermekteydi. Etyolojide en sık neden kordon prolapsusu (n=40) olup, mekonyum aspirasyon sendromu nedeniyle hipoksik-iskemik ensefalopati gelişen bebeklerde mortalite oranı anlamlı derecede yüksek (%29,40) olarak belirlendi. Mortalite riskinin bebekte kanama varlığı ile 4,6 kat, akut böbrek hasarı ile 7,3 kat, trombositopeni ile 15,5 kat, taze donmuş plazma alma durumu ile 4,6 kat ve pulmoner hemoraji ile 12,3 kat arttığı saptanmıştır. Entübe gün sayısındaki 1 birimlik artışın mortalite riskini 1,2 kat artırdığı belirlenmiştir.

Sonuç: Mekonyum aspirasyonuna bağlı hipoksik-iskemik ensefalopati gelişen vakaların ölüm oranları, mekonyum aspirasyon sendromu olmayan hipoksik-iskemik ensefalopati vakalarınkinden önemli ölçüde daha yüksekti.

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Conclusion: Mortality rates were significantly higher in cases that developed Meconium aspiration syndrome associated hypoxic-ischemic encephalopathy than in hypoxic-ischemic encephalopathy cases without meconium aspiration syndrome. A low APGAR score, increased number of intubation days, acute kidney injury, thrombocytopenia, and need for fresh frozen plasma were associated with a high risk of mortality in infants receiving therapeutic hypothermia for hypoxic-ischemic encephalopathy, and the presence of meconium aspiration syndrome significantly increased this risk.
Keywords: Hypoxic ischemic encephalopathy, meconium aspiration syndrome, newborn, mortality, therapeutic hypothermia

Düşük APGAR skoru, artmış entübasyon günü sayısı, akut böbrek hasarı, trombositopeni ve taze donmuş plazma ihtiyacı, hipoksik-iskemik ensefalopati için terapötik hipotermi alan bebeklerde yüksek mortalite riski ile ilişkilendirilmiştir ve mekonyum aspirasyon sendromu varlığı bu riski önemli ölçüde artırmıştır.

Anahtar kelimeler: Hipoksik iskemik ensefalopati, mekonyum aspirasyon sendromu, yenidoğan, mortalite, terapötik hipotermi

INTRODUCTION

The neonatal period is the most critical period of human life. The major causes of mortality during this period are prematurity, congenital malformations, early neonatal sepsis and hypoxic ischemic encephalopathy (HIE). The incidence is approximately 1-6 per 1000 live births at term[1]. It is a significant problem with serious short and long term consequences for term infants. The associated development of HIE occurs antepartum in 51%, intrapartum in 40%, and postpartum in 9%[2]. The primary event in the pathophysiology is insufficient gas exchange in the placenta or impaired ventilation at the pulmonary level because of postnatal events. Consequently, oxygen and carbon dioxide exchange is disrupted and arterial hypoxemia, hypercarbia, and acidosis develop[3]. Changes in consciousness in the acute phase [lethargy, hyperirritability, convulsions, coma, hypotonicity, hyperactive or absent tendon reflexes, decreased or absent neonatal reflexes, pupillary changes, abnormal electroencephalogram (EEG) findings] may lead to respiratory depression, multiorgan failure, sepsis, and even death[3]. By depressing myocardial functions, cardiogenic shock leads to pulmonary hypertension, mesenteric reperfusion, seizures, acute kidney injury, and death[3,4]. Hypoxic ischemic encephalopathy symptoms are seen in approximately 1.4% of live births. According to the Turkish Neonatology Society HIE Working Group Report, the mortality rate of this disease is 22.6%[4].

Therapeutic hypothermia (TH) protects brain tissue by cooling the body temperature to 33-34°C for 72 hours. Each 1°C decrease in body temperature causes a 6-10% decrease in brain metabolism. Thus, the cellular and metabolic changes leading to brain injuriy are prevented or reduced. Therapeutic hypothermia is the only current proven method in the treatment of HIE. To obtain the highest level of benefit, TH treatment must be started within the first 6 hours after birth[3].

To identify the various risk factors that influence mortality in neonates diagnosed with HIE secondary to meconium aspiration syndrome (MAS). The aim of this study was to evaluate mortality in patients with HIE receiving TH.

The present study identifies the primary risk factors contributing to increased mortality in neonates with HIE undergoing TH. It makes an important contribution to the existing literature, particularly by highlighting the impact of concomitant MAS. The study demonstrates that factors such as low APGAR [Activity, Pulse, Grimace, Appearance, Respiration] scores, prolonged intubation time, acute kidney injury, thrombocytopenia, and the need for blood product transfusion significantly increase the risk of mortality in neonates with MAS.

MATERIALS AND METHODS

Sample

The present study was conducted in the level 3 Neonatal Intensive Care Unit (NICU) of Sivas Cumhuriyet University, in a center where neonatologists and paediatricians work in collaboration. In the center, all infants diagnosed with stage 2 and 3 HIE are treated with TH. The treatment of these infants was organised and supervised by a neonatologist. The data of the cases included in the study were obtained from the medical record archives.

The sample size in the study was determined considering that mortality rates in HIE cases in the literature ranged between 12% and 28%. The 95% confidence interval was determined to be 96.

All infants included in the study were born at ≥ 36 weeks' gestation with a birth weight of ≥2000 g. Infants were excluded from the study if the diagnosis was inconclusive or if they had mild HIE, if treatment was initiated more than 6 hours postnatally, if they were born at <34 weeks' gestation, if their birth weight was <2000 g, if they had very severe or widespread parenchymal intracranial hemorrhage, life-threatening coagulopathy, or multiple organ abnormalities.

Procedure

The study protocol was approved by the Ethics Committee of Sivas Cumhuriyet University Medical Faculty (Decision No: 2019-05/03, dated: 22.05.2019).

The HIE grades of the patients were determined according to the Sarnat and Sarnat classification[5, 6]. Therapeutic hypothermia has been used in cases of grade 2 and 3 HIE. The decision for TH treatment was made according to the criteria of the Turkish Neonatology Society guidelines. These criteria were occurrence of HIE within the first 6 hours, delivery at ≥36 weeks' gestation, low APGAR score (<5 at 5 and 10 minutes), umbilical cord blood gas pH ≤7.00 or base excess more negative than -16 mmol/L in the first hour, and continuation of resuscitation in the delivery room after 10 minutes[3].

The study included 97 HIE cases who received TH treatment in the NICU of a university hospital between May 2019 and September 2022. Patient data were obtained retrospectively from the medical record archives. All incomplete records were excluded from the study. A total of 97 HIE cases were identified. The cases were evaluated in respect of mortality and two groups were formed as Group 1 (n:9, non-survivors) and Group 2 (n: 88, survivors). Infants were classified as small for gestational age (SGA) if less than the 10th percentile for gestational age, as appropriate for gestational age (AGA) if between the 10th and 90th percentiles, and as large for gestational age (LGA) if greater than the 90th percentile[7].Thrombocytopenia was defined as a platelet count <150,000 mm^3. The KDIGO (Kidney Disease Improving Global Outcomes) AKI definition is a comprehensive framework for assessing sudden declines in renal function. These criteria provide clinicians with a standardised guide to define and classify AKI, which is typically diagnosed and staged based on elevated serum creatinine or decreased urine production.

The KDIGO grading system is a comprehensive framework that defines the criteria for defining acute kidney injury (AKI). According to this system, AKI is characterised by an increase in serum creatinine levels to 1.5-1.9 times the baseline level or ≥0.3 mg/dL in stage 1 and a corresponding decrease in urine output to <0.5 mL/kg/hour within 6-12 hours. In stage 2, serum creatinine levels increase to 2.0-2.9 times the baseline level or urine output is <0.5 mL/kg/hour for ≥ 12 hours. Stage 3 is characterised by an increase in serum creatinine levels to 3 times baseline or an increase in serum creatinine to ≥4.0 mg/dl or initiation of renal replacement therapy or a decrease in eGFR to <35 mL/min/1.73 m2 in a patient younger than 18 years or <0.3 mL/kg/hour for ≥ 24 hours or anuria for ≥ 12 hours[8]. The APGAR scores at 1 and 5 minutes were evaluated by the pediatrician attending the birth[9]. Blood gas values, blood product support, and laboratory parameters of the cases were evaluated with respect to mortality.

Statistical analysis

The data obtained in the study were statistically analyzed using SPSS version 23 software (IBM SPSS, Chicago, IL, USA). The assumption of normality was assessed using the Shapiro-Wilk test. Descriptive statistics for categorical variables are presented as numbers (n) and percentages (%), while continuous variables are presented as medians (Q1-Q3). For univariate analyses of treatment outcomes (survivors vs. non-survivors), the Chi-square test, Fisher's Exact test, and Mann-Whitney U test were utilized. Logistic regression analysis was used in multivariate analysis. The independent variables that may affect mortality were cord blood gas (pH, Base Deficit), complications (bleeding, acute kidney injury, pulmonary haemorrhage, thrombocytopenia, duration of intubation days), blood product support (erythrocyte suspension, platelet suspension, fresh frozen plasma), laboratory parameters (white blood cell, haemoglobin, alanine aminotransferase, creatine kinase, uric acid). The fit of the model was evaluated by Hosmer-Lemeshow test and the test results showed that the model provided a good fit to the data (p>0.05). While determining the model, enter

method was used in variable selection. The level of statistical significance was defined as p<0.05.

RESULTS

A total of 97 HIE cases were evaluated, including 40 (41.2%) females and 57 (58.8%) males. When the infants receiving TH because of HIE were compared according to birth weight, a statistically significantly higher mortality rate was determined for the SGA and LGA infants compared to the AGA infants (p=0.006). The 5-minute APGAR score was recorded as mean 5 (4-6.50) in the non-survivors group, and as 7 (5-8) in the survivors group. The 5-minute APGAR score was determined to be significantly lower in the Group 1 infants than in Group 2 (p=0.049) (Table 1).

Table 1. Comparisons of the sociodemographic characteristics and APGAR scores of Group 1 and Group 2.

Parameters		Group 1	Group 2	P value
Type of birth, c/s (n, %)		5(55.5)	28(31.8)	0.266
Gender, female (n, %)		5(55.5)	35(39.7)	0.481
Place of birth, inborn (n, %)		3(33.3)	18(20.4)	0.402
SGA/AGA/LGA	SGA (n, %)	2(22.2)	5(5.6)	**0.006****
	AGA (n, %)	4(44.4)	78(88.6)	
	LGA (n, %)	3(33.3)	5(5.6)	
Maternal age (years), median (IQR 25-75)		31(26.50-32.50)	27(24-32)	0.200
Gestational age (weeks), median (IQR 25-75)		39(37-39)	39(38-40)	0.173
Head circumference, cm, median (IQR 25-75)		35(32-35.50)	35(34-36)	0.424
Length, cm, median (IQR 25-75)		48(45.50-49.50)	49(47.25-51.0)	0.225
Birthweight, g, median (IQR 25-75)		2769(2625-4289)	3200(2875-3500)	0.965
1-minute APGAR score, median (IQR 25-75)		3(1-4)	4(3-6)	0.095
5-minute APGAR score, median (IQR 25-75)		5(4-6.50)	7(5-8)	**0.049***

p<0.05*, p<0.01** ; Fisher's Exact Test, Mann Whitney U-test, ; NVD, normal vaginal delivery; C/S, cesarean section; AGA, appropriate for gestational age; SGA, small for gestational age; LGA, large for gestational age; APGAR, Activity, Pulse, Grimace, Appearance, Respiratory

The distributions of diagnoses such as MAS, cord prolapse, difficult birth, and placental abruption were evaluated in respect of statistical significance according to mortality in Groups 1 and 2. Accordingly, Group 1 comprised 9 (9.3%) and Group 2, 88 (90.7%) participants. MAS was determined in 5 (29.4%) patients in Group 1 and in 12 (70.6%) in Group 2 and the difference was statistically significant (p=0.035). Cord prolapse was not significant between the groups, in 2 (5%) in Group 1 and in 38 (95%) in Group 2 (p=0.509). Difficult birth was determined in 1 (2.8%) patient in Group 1 and in 35 (97.2%) in Group 2, with no significant difference between the groups (p=0.286). Placental abruption was determined in 1 (25%) in Group 1and in 3 (75%) in Group 2, and this difference was not determined to be statistically significant (Table 2).

Some characteristics of the infants in the non-survivor group are shown in Table 3.

Table 2. Evaluation of mortality according to the diagnoses

Diagnosis	Group 1(n=9)	Group 2 (n=88)	P value
MAS (n, %)	5(55.5)	12(13.6)	0.035*
Cord Prolapse (n, %)	2(22.2)	38(43.1)	0.509
Difficult Birth (n, %)	1(11.1)	35(39.7)	0.286
Placenta Abruption (n, %)	1(11.1)	3(3.4)	0.345

p<0.05* Fisher Exact Test, MAS; Meconium Aspiration Syndrome

Table 3. Some characteristics of the cases that resulted in mortality

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Gender	Male	Male	Male	Female	Female	Female	Male	Female	Female
Gestational week	36	38	39	39	40	39	39	39	36
Birthweight, gr	2750	2610	4460	2300	4300	3680	4270	2770	2640
Type of birth	C/S	C/S	NVD	NVD	C/S	NVD	C/S	NVD	C/S
Place of Birth	Inborn	Outborn	Outborn	Outborn	Inborn	Outborn	Inborn	Outborn	Outborn
Cord pH	7.03	6.75	7.01	7.00	6.95	6.95	7.04	6.85	7.07
Base deficit, mmol/L	-12.1	-21	-14.9	-12.2	-24.7	-24.8	-15	-19.8	-14
Lactate, mmol/L	17	12	7	10	12.2	16	13	10	11
1-min APGAR score	3	0	4	2	4	4	3	0	3
5-min APGAR score	4	2	5	4	5	5	4	5	5
Respiratory Support	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
LDH, U/L	4399	2416	1945	1684	2540	3270	2850	3778	1600
Creatinine Kinase, IU/L	2698	4101	4189	1489	9000	8000	3680	3682	4980
Uric Acid, mg/dL	6	10.7	7.1	5.9	8.4	9.2	7.8	5.9	8.1
Thrombocyte, /mm3	11000	78000	74000	89000	84000	108000	70000	16100	163000
Bradycardia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Seizure	No	No	No	No	No	Yes	Yes	No	Yes
HIE grade	3	3	3	3	3	3	3	3	3

NVD, normal vaginal delivery; C/S, cesarean section, LDH, Lactate dehydrogenase, HIE, Hypoxic ischemic encephalopathy
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Table 4. Evaluation of complications, cord blood gases, supportive treatment, and laboratory tests of the cases that resulted in mortality

	Parameters	**OR (95% CI)**	**P value**
Cord blood gas	pH	1.47(0.007-324.17)	0.89
	Base Deficit, mmol/L	0.661(0.26-1.67)	0.38
	Lactate, mmol/L	0.77(0.32-1.88)	0.56
Complications	Bleeding	4.54(1.11-18.58)	**0.039***
	Acute Kidney Injury	7.26(1.66-31.78)	**0.008***
	Pulmonary Hemorrhage	12.29(1.50-100.92)	**0.042***
	Thrombocytopenia, /mm3	15.47(1.85-129.51)	**0.002***
	Duration of Intubation, (days)	1.21(1.04-1.41)	**0.015***
Blood Product Support	Erythrocyte Suspension	2.51(0.45-13.95)	0.27
	Platelet Suspension	4.74(0.77-29.05)	0.12
	Fresh Frozen Plasma	4.62(1.09-19.49)	**0.048***
Laboratory	White Blood Cell, /mm3	1(1-1)	0.88
	Hemoglobin, g/L	1.171(0.49-2.77)	0.72
	Alanine Aminotransferase, IU/L	1.001(0.99-1.009)	0.76
	Creatinine Kinase, IU/L	1.001(1-1.002)	0.25
	Uric Acid, mg/dl	0.934(0.42-2.07)	0.87

p<0.05*, OR: Odds Ratio, CI; Confidence interval

Comorbid conditions increasing the risk of mortality were determined to be bleeding, acute kidney injuriy, pulmonary hemorrhage, thrombocytopenia, and the need for fresh frozen plasma. These conditions were determined to increase mortality by 4.54-fold, 7.26-fold, 12.29-fold, 15.47-fold, and 4.62-fold, respectively. An increase of 1 unit in the duration of intubation days was determined to be associated with a 1.21-fold increase in the risk of mortality ($p<0.05$). No statistically significant difference was determined in the platelet transfusion and other parameter values of pH, base deficit, white blood cells, hemoglobin, aspartate aminotransferase, creatinine kinase, and uric acid in respect of mortality (Table 4).

DISCUSSION

The diagnosis of HIE in the newborn requires a very comprehensive history and neurological examination. Prenatal, perinatal, and postnatal complications are important in respect of mortality. Some authors have also reported the need for careful evaluation of APGAR scores and the meconium status[10]. Meconium aspiration syndrome, which is frequently seen in term and post-term infants, is a potentially fatal condition causing serious respiratory complications such as pneumonia, pneumothorax, atelectasis, and persistent pulmonary hypertension. In this study, which was conducted on factors contributing to mortality, a low mean 5-minute APGAR score and a diagnosis of MAS were a significant causes of mortality.

A multicenter study by Okulu et al. included 965 patients, and respiratory tract disease associated with MAS was reported to be the postnatal problem most frequently seen (63%). Mortality did not develop in any of the infants with mild HIE cases, and was reported in 2.3% (n=13) of the cases with moderate HIE cases and in 29.8% (n=45) of those with severe HIE cases. In all the HIE cases, the mortality rate was 6%, and this rate was 8% (n=58) in grade 2-3 cases[11]. In the current study, the mortality rate of grade 2 and 3 HIE cases treated with TH was 9.2% (n=9). It is most likely that this high rate was due to the fact that many cases were referred to our center from other centers that were underequipped and lacked neonatologists.

In a study of 169 cases by Cavallin et al., the mortality rate was determined to be 23%. Among the reasons increasing mortality, there was reported to be an association with birth at another center, a low 5-minute APGAR score, depressed birth, infection within 24 hours of presentation, seizure within the first 24 hours, and the use of aminophylline during hospitalization[12].

The current study results indicate a significant difference in the incidence of MAS between Group 1 and Group 2, suggesting that distinct risk factors may contribute to the etiology of MAS. However, no significant differences were found for cord prolapse, difficult birth, or placenta abruption. This finding implies that these complications occur at similar rates in both groups. Singh et al. determined a relationship between MAS and severe morbidity and mortality. Among the pulmonary complications, air leakage (ie., pneumothorax or pneumomediastinum) was determined in 15-33% of patients with MAS[13]. The mortality rate was approximately 40% in the 1970s and this has decreased to 5-12% in the last 10 years, primarily associated with asphyxia and pulmonary hypertension[14]. It has been emphasized that changes in the application of resuscitation have contributed to the decrease in the frequency and severity of MAS[15]. Nevertheless, MAS remains a serious cause of mortality.

In a study by Tantu et al., the MAS-related neonatal mortality rate was reported to be 1.8%, and thick meconium was found to be the reason for admission to NICU in 65% of cases and contributed to all deaths. Therefore, it was emphasized that if there is meconium, there is a need for early caesarean, care to be taken in the latent stage, and an advanced level of support in NICU[16]. In another study, mortality developed in 16 (31%) of 51 infants with HIE. Advanced neonatal resuscitation, mechanical ventilation, 1-minute APGAR score, and severely abnormal EEG findings were determined to be associated with mortality[17].

Espinheira et al. determined that MAS was responsible for 1.4% of all NICU admissions. The presence of meconium was associated with severe asphyxia, and increased risk of hypoxia (58.3%), the need for mechanical ventilation support (43.1%), respiratory and/or metabolic acidosis (30.6%), pulmonary hypertension (11.1%), and increased the risk of HIE (29.2%). The mortality rate was found to be 2.8%[18]. In the current study, MAS was determined in 17.5% (n=17) of the HIE cases, and the MAS-related mortality rate of 55.5% (n=5) was statistically significant. In a study by Deveci et al., severe acidosis, abnormalities in the laboratory values measured at 24 hours (electrolyte abnormalities, hepatic and renal

dysfunction), early-onset seizures, and intubation were found to be associated with a high risk of mortality[19]. Similarly, in the current study, mortality was determined at a high rate in infants with bleeding, the need for intubation, pulmonary hemorrhage, thrombocytopenia, and acute kidney injuriy.

Widespread fibrin accumulation in the intravascular space, which can lead to tissue ischemia and necrosis, characterized by the consumption of platelets and coagulation factors formed by increased activation of the disseminated intravascular coagulation (DIC) and fibrinolytic mechanisms, is a process that includes widespread hemorrhagic diathesis and hemolytic anemia[20]. In asphyxia, cases are first exposed to hypoxia, then the risk of DIC increases due to TH. Therefore, these patients are predisposed to thrombocytopenia, factor depletion, and bleeding. Thrombocytopenia is the most common complication among hemogram parameters. Persistent pulmonary hypertension of the newborn is very common in MAS. This leads to intrapulmonary thrombocyte depletion and impaired blood oxygenation, resulting in pulmonary microthrombi and increased intrapulmonary thrombocyte activation[21]. Therefore, thrombocytopenia is secondary to hypoxia and DIC. Neonatal thrombocytopenia is most commonly associated with HIE, necrotizing enterocolitis (NEC), and infections[22]. Bleeding associated with thrombocytopenia and mortality associated with this bleeding may increase[23]. In the current study, it was determined that bleeding increased mortality by 4.54-fold, thrombocytopenia by 15.47-fold, and pulmonary hemorrhage by 12.3-fold.

In a 2007 study by Unal et al. to determine acute renal failure in newborns, acute renal failure was determined in 7.98% (n=84) of 1053 patients. Prerenal azotemia was diagnosed in 77.4% (n=65) and intrinsic acute renal failure in 22.6% (n=19) of these cases. Factors affecting mortality in newborn infants were determined to be prematurity, intrinsic acute renal failure, and mechanical ventilation[24]. In the current study, intubation and acute kidney injuriy were determined to increase the risk of mortality in cases diagnosed with HIE. As a result of a sudden deterioration in kidney functions in asphyxia, mortality increases as fluid electrolyte and acid-base balance cannot be provided, blood pressure cannot be regulated, and nitrogen breakdown products cannot be eliminated from the body. As the kidney functions in patients with asphyxia can deteriorate from both the disease itself and secondary to TH, it is recommended that care is taken in respect of intrinsic kidney injuriy in particular and subsequent prerenal kidney injuriy. In the current study, acute kidney injuriy increased mortality 7.26-fold.

Mortality is also increased when ventilation support is insufficient, when there is no sufficiently effective ventilator support for newborns being transported, and when the necessary care in ventilator application cannot be provided by trained personnel. Reducing invasive interventions and care taken in respect of sterilization decreases mortality in newborns on ventilation[25]. The current study results showed that an increase of 1 day in the duration of intubation raised mortality by 1.21-fold. Therefore, the need to closely monitor intubated HIE patients must be emphasized.

Limitations of this study include the relatively small number of patients, the single-center nature of the study, and the lack of data regarding transport of cases accepted from multiple centers for hypothermia. Because there was no pediatric cardiologist available, patients were referred to the pediatric cardiology outpatient clinic after discharge. Some patients with congenital heart disease and persistent pulmonary hypertension were seen by a pediatric cardiologist at another hospital. In addition, the patients' amplitude EEG data were incomplete and were not included in the evaluation.

In the association of MAS and HIE, the mechanisms leading to an increased risk of mortality could be studied in detail. In addition to TH, supportive therapies (e.g., anti-inflammatory or neuroprotective agents) administered to infants with MAS could be tested. The effect of these therapies on mortality and neurodevelopmental outcomes can be analyzed. Prospective studies with large sample groups in different centers can be performed to confirm risk factors for mortality in infants with MAS and HIE and to obtain generalizable results.

In conclusion, the mortality rates of cases that developed MAS-associated HIE were significantly higher than those of HIE cases without MAS. A low APGAR score, increased number of intubation days, acute kidney injury, thrombocytopenia, and need for fresh frozen plasma were associated with a high risk of mortality in infants receiving TH for HIE, and the presence of MAS significantly increased this risk. Therefore, considering that the prognosis may be worse when MAS is present as an etiologic factor in

patients to be treated with TH, careful follow-up of these patients is recommended.

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