ORIGINAL ARTICLE

PREVALENCE AND DETERMINANTS OF HYPOXIC-ISCHEMIC ENCEPHALOPATHY IN PERINATAL ASPHYXIA POPULATION OF DISTRICT MARDAN, PAKISTAN

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Background: Neonatal encephalopathy is a diverse and clinically well-known syndrome. The objectives of this study were to determine the prevalence and determinants of hypoxic-ischemic encephalopathy (HIE) in perinatal asphyxia population of District Mardan, Pakistan.

Materials & Methods: This cross-sectional study was conducted in Department of Pediatrics, Bacha Khan Medical College, Mardan, Pakistan from 1st January 2017 to 30th June 2017. 160 term neonates with perinatal asphyxia were included. Sex, age groups, gestational age, mode of delivery, weight groups and presence of HIE were variables. Presence of HIE was dependent while five demographic variables were independent variables respectively for five chi-square tests of association.

Results: Mean age of sample of 160 infants was 2.537 ± 1.26 (1-7, range 6) days, mean gestational age was 38.681 ± 1.24 weeks and mean weight 3.275 ± 0.36 kg. Out of 160 infants with perinatal asphyxia, 16 (8.16%, 95%CI 7.35-13.46) had HIE (HIE). These positive 16 cases included 11 (6.88%) boys & 5 (3.12%) girls, 15 (9.38%) of 1-3 & one (0.62%) of 4-7 days, 14 (8.75%) of gestational age 37-39 & two (1.25%) of >39 weeks, 15 (9.38%) with vaginal delivery & one (0.62%) with C-section and 14 (8.75%) of ≤3 & two (1.25%) of >3 kg weight groups. There was association between presence of HIE and weight groups, but not with sex, age groups, gestational age and mode of delivery.

Conclusion: We found 10% prevalence of HIE in perinatal asphyxia population of District Mardan, Pakistan. The prevalence was higher in boys than girls, in age group 1-3 days than 4-7 days, in gestational age ≤37-39 than >39 weeks, in vaginal than C-section delivery and in weight group ≤3 kg than >3 kg group. There was association between presence of HIE and weight groups, but not with sex, age groups, gestational age and mode of delivery.

KEY WORDS: Perinatal Asphyxia; Hypoxic-Ischemic Encephalopathy, Prevalence; Distribution; Adult; Sex; Age Groups; Gestational Age; Association; Chi-square Test of Association.

1. INTRODUCTION

1.1 Background: Neonatal encephalopathy is a diverse and clinically well-known syndrome. Neonates have disturbed neurologic functions in this syndrome in the earliest days of life. It is shown by reduction in level of consciousness and seizures together with difficulty in initiation and maintenance of respiration and reflexes and tone depression.[1]

Wide range of disorders can cause neonatal encephalopathy. For some cases of neonatal encephalopathy (HIE), birth asphyxia is accountable, but this is not same for all. This is challenging to determine whether event of acute hypoxic-ischemia has contribution in neonatal encephalopathy as for their diagnosis no gold standard testing is available. Low Apgar scores, neonatal seizures and low cord pH are the numerous clinical signs of hypoxic-ischemic encephalopathy while encephalopathy occur nonspecifically and might happen in the

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absence of long-term neurologic sequelae and global hypoxic-ischemic brain injury. Though, when hypoxic-ischemic encephalopathy is suggested as a most likely cause by clinical symptoms, then "presumed HIE" is frequently appropriate diagnosis, whereas waiting for results of additional tests and starting therapies of neuroprotection aimed exactly to treat hypoxic-ischemic encephalopathy (HIE).[2]

The neonatal encephalopathy incidence is dependent on how to define syndrome, however the estimated prevalence varies between 2-9/ 1000 term births.[3-6] In the US population it was shown in a report that between the years 1991 and 2000, the diagnosis of "birth asphyxia" was declined.[3] Kurinczuk, et al.[7] reported in 2010, the estimated incidence of neonatal encephalopathy of 3 per 1000 (95%CI 2.7 to 3.3) live birth, and of hypoxic-ischemic encephalopathy as 1.5 per 1000 (95%CI 1.3 to 1.7) live births.

Palsdottir K, et al.[8] from Reykjavik, capital city of Iceland, reported birth asphyxia as 9.4 per 1000 live births and HIE as 1.4 per 1000 live term births for the period from 1997 to 2001. Aliyu, et al.[9] reported 257 (24.7%) cases of birth asphyxia out 1040 admissions to special care baby unit.

Padayachee, et al.[10] from Johannesburg, South Africa showed the rate of perinatal asphyxia (5-minute Apgar score <6) as 4.7 per 1000 live births, and the evidence of hypoxic ischaemic encephalopathy (HIE) in 3.6 per1000 live births for the period from 1-1-2006 to 31-12-2011.

Athuman Juma[11] from Dar Es Salaam, Tanzania in 2007 reported 362 admitted neonates. Out of these, 112 (30.9) had birth asphyxia. Out of these 112 cases with birth asphyxia, 92 (82.1%) had HEI.

Simiyu, et al.[12] from Tanzania reported 1752 newborns for the period from Nov. 2014 to Apr. 2015. Of these newborns, 201 (11.5%) had birth asphyxia which was defined by an APGAR score less than 7 at 5 min after birth. Of the 201 newborns with asphyxia, 187 had hypoxic ischemic encephalopathy (HIE) giving a prevalence of 10.7% (187*100/1752=10.7).

Between years 2000 and 2008 prevalence of HIE in Spain was reported to be 1.088 per 1000 live births, and the incidence of clinically significant HIE (moderate and severe grades) was reported as 0.49 per 1,000 live births.[13]

1.2 Research Problems (RPs), Knowledge Gaps (KGs), Research Questions (RQs) & Rationale: Unawareness about the prevalence and determinants (association to sex, age groups, gestational age, mode of delivery and weight respectively) of hypoxic-ischemic encephalopathy (HIE) in perinatal asphyxia population of District Mardan, Pakistan are our six RPs. Unavailability of information regarding these six RPs are our six KGs and rationale for our study. What will be the prevalence, and determinants of HIE in perinatal asphyxia population of District Mardan, Pakistan are our six research questions.

1.3 Research Objectives (ROs)

RO 1: To determine the prevalence of HIE in perinatal asphyxia population of District Mardan, Pakistan.

RO 2-6: To determine the association between the presence of HIE and sex, age groups, gestational age, mode of delivery and weight respectively in perinatal asphyxia population of District Mardan, Pakistan.

1.4 Research (Null) Hypotheses

H_{01}: There is no good fit between the observed and expected prevalence of HIE in perinatal asphyxia population of District Mardan, Pakistan (RQ 1)

H_{02}: There is no association between the presence of HIE and sex in perinatal asphyxia population of District Mardan, Pakistan (RQ 2)

H_{03}: There is no association between the presence of HIE and age groups in perinatal asphyxia population of District Mardan, Pakistan (RQ 3)

H_{04}: There is no association between the presence of HIE and gestational age at birth in perinatal asphyxia population of District Mardan, Pakistan (RQ 4)

H_{05}: There is no association between the presence of HIE and mode of delivery in perinatal asphyxia population of District Mardan, Pakistan (RQ 5)

H_{06}: There is no association between the presence of HIE and weight in perinatal asphyxia population of District Mardan, Pakistan (RQ 6)

2. MATERIAL AND METHODS

2.1 Study Design, Settings & Duration: This cross-sectional study was done at the Department of Pediatrics, Bacha Khan Medical College, Mardan, Pakistan from 1st January 2017 to 30th June 2017. The sample data was collected from the Pediatric Unit of Mardan Medical Complex, Mardan, Pakistan. The study was approved from the Institutional Ethical Review Committee. Consent of the patients' parents was obtained before inclusion in the study.

2.2 Population, Sample Size & Technique and Sample Selection: District Mardan is the second populous district of Khyber Pakhtunkhwa; a north-western province of Pakistan. Its population was 1,460,000 in 1998 Census. For start of year 2017, it was estimated to be around 2,300,000. With presumed 1% contribution from early neonates, it would be 23,000 population of early neonates; out of this 1% i.e. 2,300 are presumed with perinatal asphyxia; our population at risk. With this much population, expected prevalence rate of 5% in this population, margin of error 3.26% and confidence interval of 95%, sample size came to be 160 using

online calculator Raosoft®.[14] Non-probability consecutive sampling technique was used in our study.

The criteria of inclusion was all term infants (gestational age > 36 weeks on LMP at birth) with perinatal asphyxia in early neonatal period (7 days of birth), while the exclusion criteria were encephalopathy associated with preterm birth, congenital abnormalities on ultrasound, a major single-organ anomaly on ultrasound, patients with evidence of antenatal events causing prenatal injury such as prolonged loss of fetal movements on medical record.

2.3 Conduct of Procedure: All these neonates were admitted and standard protocols were followed for their management.

2.4 Data Collection Plan: Age in days, gestational age in weeks, weigh in kg, sex (boys, girls), age groups (1-3, 4-7 days), gestational age (37-39, >39 weeks), mode of delivery (vaginal, C-section) and weight groups (≤3, >3 kg) were demographic variables (attributes), while presence of HIE (yes/ no) was a single research variable (attributes). The data was measured on nominal scale for all the variables, except ratio (numeric) for age in days, gestational age in weeks and weigh in kg. The presence of HIE was a dependent variable, while sex, age groups, gestational age at birth, mode of delivery and weight groups were independent variables respectively for each of the five tests of association.

2.5 Data Analysis Plan

2.5.1 Descriptive Statistics and Estimation of Parameters: All the ratio variables were analyzed by mean & SD. The five nominal variables were analyzed by count and percentage for the sample. The estimated parameters for the population were stated as CI (confidence intervals) for proportion at 80%CL using Wilson score interval by proportion CI calculator.[15]

2.5.2 Hypotheses Testing: The observed prevalence was compared to the expected prevalence of HIE using chi-square goodness of fit test (H_{01}).[16-18] The associations between the presences of HIE and its five determinants were testified by using chi-square test of association (H_{02-6}).[16,17,19]

3. RESULTS

3.1 Descriptive Statistics & Estimation of Parameters

3.1.1 Sample description & prevalence of HIE in infants with perinatal asphyxia: Mean age of the sample of 160 infants was 2.537±1.26 (1-7, range 6) days, mean gestational age at birth was 38.681±1.24 weeks and mean weight was 3.275±0.36 kg.

Out of 160 infants with perinatal asphyxia, 113 (70.6%) were boys and 47 (24.4%) girls, 155 (96.88%) were in age group 1-3 days and 5 (3.12%) in age group 4-7 days, 137 (85.62%) had gestational age at birth of 37-39 weeks and 23 (14.38) had >39 weeks, mode of delivery was vaginal in 123 (76.78) and C-section in 37 (23.12) cases and by weight groups 21 (13.12) were in ≤3 kg and 139 (86.88) in >3 kg weight group.

Out of 160 infants with perinatal asphyxia, 16 (8.16%) had HIE, while 144 (91.84%) had no HIE. (Table 3.1.1)

3.1.2: Distribution of positive cases of hypoxic-ischemic encephalopathy (HIE) in perinatal asphyxia: Table 3.1.2 shows the distribution of 16 positive neonates with HIE. The prevalence of HIE is higher in boys than girls, in age group 1-3 days than 4-7 days, in gestational age ≤37-39 than >39 weeks, in vaginal than C-section delivery and in weight group ≤3 kg than >3 kg group.

3.2 Hypotheses Testing

3.2.1: Observed vs. expected prevalence of HIE (RQ1, H_{01}): For our population, we were expecting 32 cases of HIE out of 160 cases of birth asphyxia. The observed cases were 16 out of 160. These are compared through chi-square goodness-of-fit test.

Table 3.1.1: Prevalence of hypoxic-ischemic encephalopathy (HIE) in perinatal asphyxia population of District Mardan, Pakistan (n=160)

Variable	Attributes	Sample statistics		80%CI for proportion	
		Count	Percentage	Lower	Upper
Presence of HIE	Yes	16	10 %	07.35	13.46
	No	144	90 %	86.54	92.64
	Total	160	100	Population parameters	

With p-value <.0157, H_{01} was rejected, showing that the observed prevalence of HIE in birth asphyxia in our population is lower than expected. (Table 3.2.1)

3.2.2 Association of presence of HIE to sex: Chi-square test of association showed that there is no association between the presence of HIE to sex in perinatal asphyxia population of District Mardan. (Table 3.2.2)

3.2.3 Association of HIE to age groups: Chi-square test of association showed that there is no association between the presence of HIE to age groups in perinatal asphyxia population of District Mardan. (Table 3.2.3)

3.2.4 Association of presence of HIE to gestational age at birth: Chi-square test of association showed that there is no association between the presence of

Table 3.1.2: Distribution of positive cases of hypoxic-ischemic encephalopathy (HIE) in perinatal asphyxia population of District Mardan, Pakistan (n=160)

S. No.	Variables	Attributes	Sample size	Sample statistics		80% CI for proportion	
				Count	Percentage	Lower	Upper
1	Sex	Boys	113	11	06.88	04.72	09.90
		Girls	047	05	03.12	01.78	05.41
2	Age groups	1-3 days	155	15	09.38	06.82	12.75
		4-7 days	005	01	00.62	00.18	02.06
3	Gestational age	37-39 weeks	137	14	08.75	06.29	12.05
		>39 weeks	023	02	01.25	00.52	02.97
4	Mode of delivery	Vaginal	123	15	09.38	06.82	12.75
		C-section	037	01	00.62	00.18	02.06
5	Weight groups	≤ 3 kg	021	14	08.75	06.29	12.05
		> 3 kg	139	02	01.25	00.52	02.97
Total			160	16	10%	Population parameters	

Table 3.2.1: Observed vs. expected prevalence of hypoxic-ischemic encephalopathy (HIE) in perinatal asphyxia population of District Mardan, Pakistan (n=160)

Variable	Attributes	O	E	O-E	$(O-E)^2$	$(O-E)^2/E$	$\sum\chi^2$	d.f.	p-value
Presence of HIE	Yes	16	32	-16	625	8	10	1	.0157
	No	144	128	16	625	2	H_{01} accepted at alpha .05		
	Total	160	160		Chi-square goodness of fit with Yates correction				

O= Observed count, E= Expected count, χ^2= chi-square statistic, d.f.= degree of freedom

Table 3.2.2 Association of presence of hypoxic-ischemic encephalopathy (HIE) to sex in perinatal asphyxia population of District Mardan, Pakistan (n=160)

Variable/ Attributes	Presence of HEI						Rows Total	$\sum\chi^2$	d.f.	p-value
	Yes			No						
Sex	O	(E)	$[\chi^2]$	O	(E)	$[\chi^2]$	$\chi2$ test of association with Yates correction			
Men	11	(11.3)	[0.01]	102	(101.7)	[0]	113	0.0134	1	.90788
Women	5	(4.7)	[0.02]	42	(42.3)	[0]	47			
Columns Total	16			144			160	H_{02} accepted at alpha 0.05		

O= Observed count, E= Expected counts, χ^2= chi-square statistic, d.f.= degree of freedom

HIE to gestational age at birth in perinatal asphyxia population of District Mardan. (Table 3.2.4)

3.2.5 Association of presence of HIE to mode of delivery: Chi-square test of association showed that there is no association between the presence of HIE to mode of delivery in perinatal asphyxia population of District Mardan. (Table 3.2.5)

3.2.6 Association of presence of HIE to weight groups: Chi-square test of association showed that there is association between the presence of HIE to weight groups at birth in perinatal asphyxia population of District Mardan. (Table 3.2.6)

Table 3.2.3 Association of presence of hypoxic-ischemic encephalopathy (HIE) to age groups in perinatal asphyxia population of District Mardan, Pakistan (n=160)

Variable/ Attributes	Presence of HEI						Rows Total	$\sum\chi^2$	d.f.	p-value
	Yes			No			χ^2 test of association with Yates correction			
Age groups	O	(E)	[χ^2]	O	(E)	[χ^2]				
1-3 days	15	(12.4)	[0.55]	109	(111.6)	[0.06]	124	1.7363	1	.18509
4-7 days	1	(3.6)	[1.88]	35	(32.4)	[0.21]	36			
Columns Total	16			144			160	H_{03} accepted at alpha 0.05		

O= Observed count, E= Expected counts, χ^2= chi-square statistic, d.f.= degree of freedom

Table 3.2.4 Association of presence of hypoxic-ischemic encephalopathy (HIE) to gestational age at birth in perinatal asphyxia population of District Mardan, Pakistan (n=160)

Variable/ Attributes	Presence of HEI						Rows Total	$\sum\chi^2$	d.f.	p-value
	Yes			No			χ^2 test of association with Yates correction			
Gestational age at birth	O	(E)	[χ^2]	O	(E)	[χ^2]				
37-39 weeks	14	(13.7)	[0.01]	123	(123.3)	[0]	137	0.0226	1	.88058
> 39 weeks	2	(2.3)	[0.04]	21	(20.7)	[0]	23			
Columns Total	16			144			160	H_{04} accepted at alpha 0.05		

O= Observed count, E= Expected counts, χ^2= chi-square statistic, d.f.= degree of freedom

Table 3.2.5 Association of presence of hypoxic-ischemic encephalopathy (HIE) to mode of delivery in perinatal asphyxia population of District Mardan, Pakistan (n=160)

Variable/ Attributes	Presence of HEI			Rows Total	$\sum\chi^2$	d.f.	p-value
	Yes	No		χ^2 test of association with Yates correction			
Mode of delivery	O (E) [χ^2]	O (E) [χ^2]					
Vaginal	15 (12.3) [0.59]	108 (110.7) [0.07]		123	1.8907	1	.169126
C-section	1 (3.7) [1.97]	36 (33.3) [0.22]		37			
Columns Total	16	144		160	H_{05} accepted at alpha 0.05		

O= Observed count, E= Expected counts, χ^2= chi-square statistic, d.f.= degree of freedom

Table 3.2.6 Association of presence of hypoxic-ischemic encephalopathy (HIE) to weight groups in perinatal asphyxia population of District Mardan, Pakistan (n=160)

Variable/ Attributes	Presence of HEI			Rows Total	$\sum\chi^2$	d.f.	p-value
	Yes	No		χ^2 test of association with Yates correction			
Weight	O (E) [χ^2]	O (E) [χ^2]					
≤ 3 kg	14 (2.1) [67.43]	7 (18.9) [7.49]		21	79.1504	1	<.00001
> 3 kg	2 (13.9) [10.19]	137 (125.1) [1.13]		139			
Columns Total	16	144		160	H_{06} rejected at alpha 0.05		

O= Observed count, E= Expected counts, χ^2= chi-square statistic, d.f.= degree of freedom

4. DISCUSSION

4.1 Prevalence of hypoxic-ischemic encephalopathy (HIE) in perinatal asphyxia population:

Neonatal encephalopathy is a diverse and clinically well-known syndrome. It is shown by reduction in level of consciousness and seizures together with difficulty in initiation and maintenance of respiration and reflexes and tone depression.[1]

Our study showed the prevalence of HIE in neonatal asphyxia as 10% (80% CI 7.35-13.46). Kurinczuk, et al.[7] reported in 2010, the estimated incidence of neonatal encephalopathy of 3 per 1000 (95%CI 2.7 to 3.3) live birth, and of hypoxic-ischemic encephalopathy as 1.5 per 1000 (95%CI 1.3 to 1.7) live births. Palsdottir K, et al.[8] from Reykjavik, Iceland, reported birth asphyxia in 9.4 per 1000 live births and HIE in 1.4 per 1000 live term births for years 1997 to 2001. Aliyu, et al.[9] reported 257 (24.7%) cases of birth asphyxia out 1040 admissions to special care baby unit.

Padayachee, et al.[10] from Johannesburg, South Africa showed the prevalence of perinatal asphyxia as 4.7 per 1000 live births, and the evidence of hypoxic ischaemic encephalopathy (HIE) in 3.6 per1000 live births for the period from 2006 to 2011.

Athuman Juma[11] from Dar Es Salaam, Tanzania in 2007 reported 362 admitted neonates. Out of these, 112 (30.9) had birth asphyxia. Out of these 112 cases with birth asphyxia, 92 (82.1%) had HEI.

Simiyu, et al.[12] from Tanzania reported 1752 newborns for the period from Nov. 2014 to Apr. 2015. Of these newborns, 201 (11.5%) had birth asphyxia. Of the 201 newborns with asphyxia, 187 had hypoxic ischemic encephalopathy (HIE) giving a prevalence of 10.7% (187*100/1752=10.7).

Between years 2000 and 2008 prevalence of HIE in Spain was reported to be 1.088 per 1000 live births, and the incidence of clinically significant HIE (moderate and severe grades) was reported as 0.49 per 1,000 live births.[13]

4.2 Distribution of positive cases of HIE in perinatal asphyxia population by sex, age groups, gestational age, mode of delivery and weight groups:

No relevant studies were available on distribution on net searched on different engines, databases and websites. Our study is an innovative attempt. It will provide baseline data for future research.

4.3 Association of presence of HIE to sex, age groups, gestational age, mode of delivery and weight groups in perinatal asphyxia population:

No relevant studies were available on distribution on net searched on different engines, databases and websites. Our study is an innovative attempt. It will provide baseline data for future research.

CONCLUSION

We found higher prevalence of hypoxic-ischemic encephalopathy (HIE) in perinatal asphyxia population of District Mardan, Pakistan than many other populations. The prevalence was higher in boys than girls, in age group 1-3 days than 4-7 days, in gestational age ≤37-39 than >39 weeks, in vaginal than C-section delivery and in weight group ≤3 kg than >3 kg group. There was association between presence of HIE and weight groups, but not with sex, age groups, gestational age and mode of delivery.

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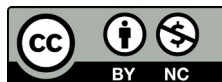
AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	KU, MN, SS
Acquisition, Analysis or Interpretation of Data:	KU, MN, SS, MQK, KA, QK
Manuscript Writing & Approval:	KU, MN, SS, MQK, KA, QK

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.