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"Acute Complications in neonates with birth asphyxia undergoing therapeutic hypothermia"-A Cross sectional observational study in a tertiary teaching hospital in kolar.

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ABSTRACT

India carries the largest burden of neonatal deaths worldwide, and perinatal asphyxia and Hypoxic ischemic encephalopathy (HIE) account for a quarter of these deaths and an unknown number of survivors with lifelong disability.The aim of the study is to determine the acute complications occurring in neonates with birth asphyxia undergoing therapeutic hypothermia in a tertiary care hospital in Kolar.A cross sectional observational study was done from May 2021 to June 2022 and neonates with birth asphyxia were included in the study. Acute complications occurring in these neonates were analyzed based on the clinical and laboratory parameters. p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests. Out of 23 birth asphyxia neonates included in the study, the mean age of the neonates was 76.52$\pm$87.7 minutes. 14(60.9%) were males and 9(39.1%) were females with 3(13%) being <2.5kg and 20 $\geq$2.5kg. Thompson score used in this study to assess the neurological status ranged between 8 and 13 with mean value of 10.26$\pm$1.25. Among the clinical parameters, sinus bradycardia and cardiac arrhythmia($p<0.05$) had statistically significant association with outcome of neonates who underwent therapeutic cooling. Thrombocytopenia ($p<0.05$) and Culture proven sepsis($p<0.05$) were the laboratory parameters which had statistically significant association with outcome. This study reveals that Therapeutic hypothermia does not increase mortality in birth asphyxia infants. However, complications like sinus bradycardia, cardiac arrhythmia, thrombocytopenia requiring platelet transfusion and culture sepsis were commonly observed in neonates who received therapeutic cooling.

Key words: Complications, neonates, survival

INTRODUCTION

Perinatal asphyxia stands as a significant concern all around the world. According to World Health Organisation reports, the incidence of perinatal asphyxia is around 6-10 new-borns in 1000 live births.[1] Perinatal asphyxia is a condition in which impairment of blood gas exchange occurs that results in hypoxemia and hypercapnia. It is important to have quick resuscitation measures for perinatal asphyxia as it will lead to various complications. Hypoxia and ischemia together result in biochemical changes that lead to brain neuronal death and damage. Permanent brain injury is the most severe long-term consequence of perinatal asphyxia. The phenomenon of Multiorgan dysfunction (MOD) in neonates with perinatal asphyxia is associated to the plunging reflex wherein blood flow to vital organs is preserved at the cost of nonvital organs. The amalgamation of reduced blood flow and hypoxemia can pledge a cascade of physiological irregularities that backgrounds injuries to multiple organs. When

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MOD occurs, it is renowned that asphyxiated infants with Hypoxic ischemic encephalopathy (HIE) initiations the diving reflex that results in hypoxic and ischemic injury even to vital organs.[2] Neonatal Encephalopathy (NE) is an abnormal neurological position due to extensive CNS injury which arises as a sequence of events in a neonate. [3]

Therapeutic hypothermia is the gold standard treatment to reduce death or disability in infants with moderate to severe hypoxic-ischemic encephalopathy (HIE).[2]Therapeutic hypothermia is initiated within 6 hours of birth with the target temperature being 33.5˚C (acceptable range is 32.5˚C to 34.5˚C) and continued for 72 hours of age in ICU by setting gradual rewarming at the rate of 0.5˚c every 2 hours until the baby's core temperature is 36.5˚C over 10 to 12 hours.[1] Mechanisms of action of Therapeutic hypothermia include1) Decreased energy utilization and severity of secondary energy failure 2)Suppression of free radical induced injury 3)Reduction in the extent of brain injury 4)Inhibition of inflammation and resultant release of cytokines.[4]

By considering all the facts, the aim of the study is to determine the acute complications occurring in neonates with birth asphyxia undergoing therapeutic hypothermia in a tertiary care hospital in Kolar and to determine the clinical and laboratory parameters that require careful monitoring to reduce the occurrence of multiorgan complications in neonates undergoing therapeutic hypothermia.

MATERIALS AND METHODS

This is a cross sectional observational study conducted during May 2021 to June 2022. All neonates with birth asphyxia and underwent therapeutic hypothermia were considered for the study. Neonates with gestational age more than or equal to 36 weeks, having birthweight more than or equal to 2kg with evidence of birth asphyxia and features of neonatal encephalopathy within 6 hours of birth were included for the present study. Neonates with presence of lethal chromosomal abnormalities and with congenital anomalies were excluded from the present study. Whole body cooling (miracradle) is used in our hospital and therapeutic cooling is initiated within 6 hours for the asphyxiated neonates and target temperature is 33.5˚c(33-34˚c) with the acceptable range being 32.5-34.5˚c.

All baseline investigations were done before starting therapeutic cooling. Cardiac monitor should be connected and catheterisation should be done.

American academy of Paediatrics and American academy of Obstetrics and Gynaecology defined Perinatal asphyxia as presence of the following criteria: Profound metabolic acidosis(pH<7) in umbilical cord blood, Apgar score <3 at 5 minutes, signs of neonatal encephalopathy like seizures, encephalopathy, tone abnormalities and evidence of multiorgan involvement. [5]

Temperature: Core body temperature (rectal) of the neonate was recorded continuously and documented every 15 minutes until the target temperature is reached and then hourly. During rewarming core temperature was recorded continuously and recorded every hour.

Respiratory status: Arterial blood gas and serum lactate were monitored at baseline and then at 4,8,12,24,48 and 72 hours of time and as when clinically indicated.

Cardiovascular system: ECG leads were connected and the vitals were monitored regularly.

Fluid, electrolyte balance and renal/gastrointestinal system: Neonates were kept Nothing by mouth (NPO) from when passive cooling started until rewarmed to normal temperature. Glucose, serum electrolytes with calcium, RFT, AST/ALT were monitored at baseline and then at 24, 48 and 72 hours of treatment and when clinically indicated. To avoid cerebral oedema in this at-risk population, goal sodium should be at high end of normal range. As most of these neonates have decreased urine output of multifactorial aetiology, need for fluid restriction will assist in avoiding serum sodium below 140.

Coagulopathy:

Coagulation profile (Prothrombin time, activated partial thromboplastin time, INR) and platelet count were measured daily and when clinically indicated. Coagulopathy was treated as per routine with Fresh frozen plasma.

Infections:

Baseline CBC, CRP and blood culture were obtained. Antibiotics (1st line) was started and later hiked based on the reports. CRP being elevated more than 6 was considered as probable sepsis and blood culture revealing growth was considered as culture proven sepsis.

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From these observations it was concluded which complications were commonly associated with therapeutic cooling and these can be given additional care in the future. Precautions should take to prevent these complications from occurring and management protocols to treat these complications can be framed.

Neurological status: Neurological status of the neonates was assessed using Thomson score in our study.

Table 1: Thompson score for neonates

Sign	0	1	2	3
Tone	Normal	Hypertonia	Hypotonia	Flaccid
LOC	Normal	Hyperalert, Stare	Lethargic	Comatose
Fits	None	<3/day	>2/day	-
Posture	Normal	Fisting, Cycling	Strong distal flexion	Decerebrate
Moro	Normal	Partial	Absent	-
Grasp	Normal	Poor	Absent	-
Suck	Normal	Poor	Absent+Bites	-
Respiration	Normal	Hyperventilation	Brief Apnea	IPPV(Apnea)
Fontanel	Normal	Full, not tense	Tense	
Maximum score: 22, Mild HIE: 1-10, Moderate HIE:11-14, Severe HIE:15 LOC: Level of Consciousness				

Statistical analysis

Data were entered into Microsoft excel and was analysed using SPSS 22 version software. Kolmogorov–Smirnov test and the Shapiro–Wilk test were used for normality. Chi-square test was used to find significance for qualitative data. Fischer's exact test was used for significance for qualitative data. p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests. [6-8]

RESULTS

In our study, 23 neonates with birth asphyxia who underwent therapeutic cooling were included with mean age of 76.52 ± 87.70 minutes.

Table 2: Distribution of study subjects based on gender

Characteristics		Frequency (N)	Percentage (%)
Gender	**Male**	14	60.9%
	Female	9	39.1%

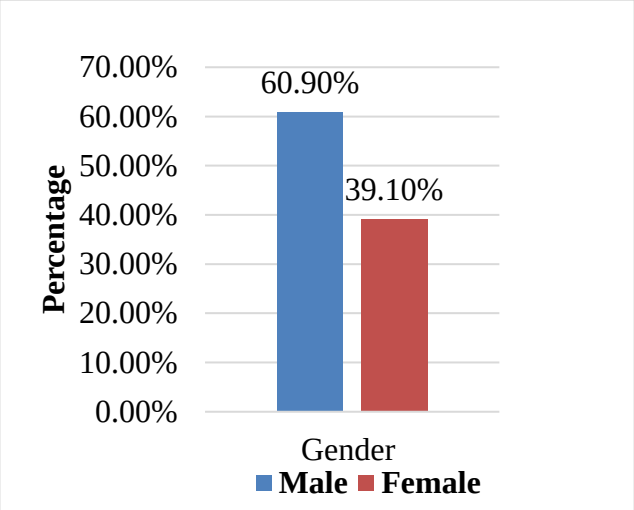

Fig 1. Distribution of study subjects based on gender

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Table 2 and Figure 1 shows the distribution of study subjects based on gender. Among the 23 birth asphyxia neonates 14(60.9%) were males and 9(39.1%) were females.

Table 3: Distribution of study subjects based on birth weight

Characteristics		Frequency (N)	Percentage (%)
Birth Weight	**<2.5 kg**	3	13.0%
	≥2.5 kg	20	87.0%

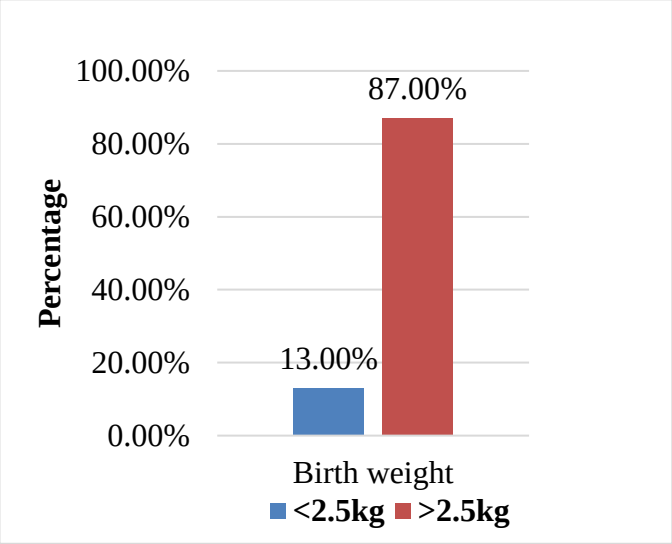

Fig 2. Distribution of study subjects based on birth weight

Table 3 and Figure 2 shows the Distribution of study subjects based on birth weight. The mean birth weight was estimated to be 2.86 ± 0.42 kg and 3(13.0%) were <2.5 kg and 20(87%) were ≥2.5kg.

Table 4: Distribution of study subjects based on Mode of delivery

Characteristics		Frequency (N)	Percentage (%)
Mode of Delivery	**Normal Vaginal**	6	26.1%
	Instrumental	2	8.7%
	Caesarean Section	15	65.2%

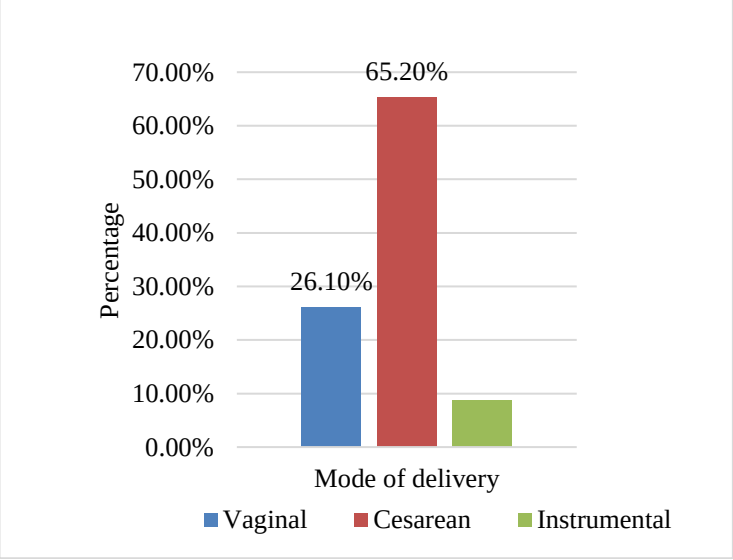

Fig 3. Distribution of study subjects based on Mode of delivery

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Table 4 and Figure 3 shows the Distribution of study subjects based on Mode of delivery. Among the 23 birth asphyxia neonates,6(26.1%) was delivered by Normal vaginal delivery, 2(8.7%) by instrumental delivery and 15(65.2%) by Caesarean section. Caesarean section was however the most common mode of delivery.

Table 5: Distribution of study subjects based on Place of delivery

Characteristics		Frequency (N)	Percentage (%)
Place of Delivery	**Inborn**	15	65.2%
	Outborn	8	34.8%

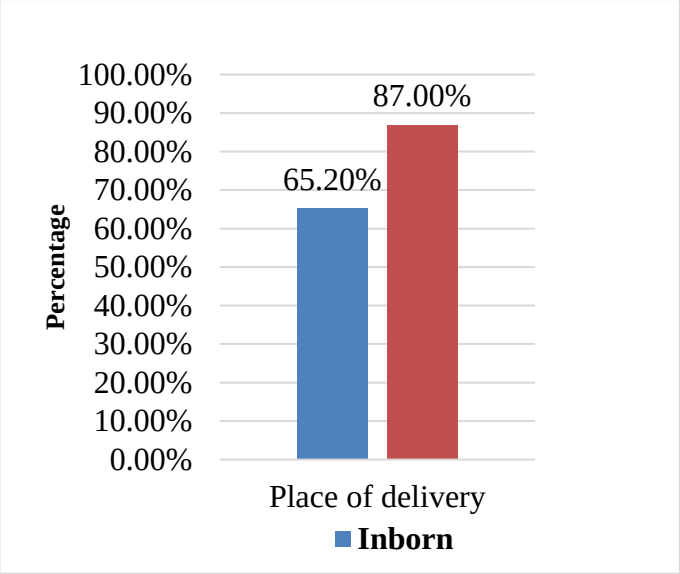

Fig 4. Distribution of study subjects based on Place of delivery

Table 5 and Figure 4 shows the Distribution of study subjects based on Place of delivery. 15(65.2%) were inborn neonates delivered in our hospital whereas 8(34.8%) were delivered in outside hospital and were referred.

Table 6: Distribution based on APGAR Score of the study subjects at 1 and 5 minutes

APGAR Score		Frequency (N)	Percentage (%)
At 1 minute	**<3**	22	95.7%
	<5	1	4.3%
At 5 minutes	**<3**	3	13.0%
	<5	20	87.0%

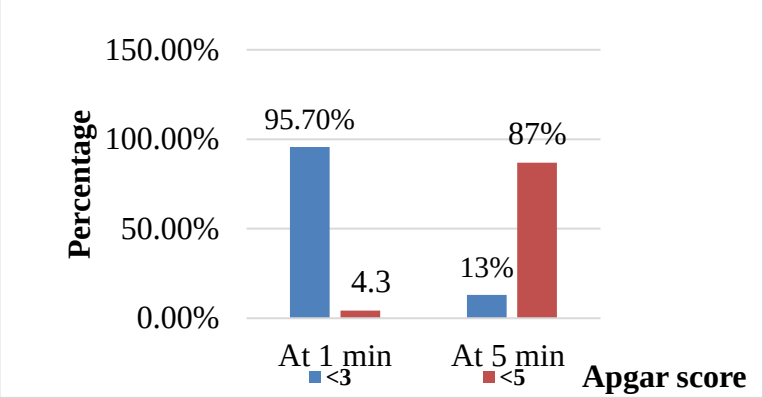

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Fig 5. Distribution based on APGAR Score of the study subjects at 1 and 5 minutes

Table 6 and Figure 5 shows the Distribution of the study subjects based on APGAR Score at 1 and 5 minutes. Apgar score was <3 at 1 minute in 22(95.7%) and <5 in 1(4.3%) neonates whereas it was <3 at 5 minutes in 3(13%) and <5 in 20(87%) neonates. The mean APGAR score was 2.61 ± 0.66 at 1 minute, which got improved to 4.22 ± 0.67 at 5 minutes.

At admission, the Thompson score was assessed among the neonates, which ranged between 8 and 13, with the mean value of 10.26 ± 1.25. The mean pH of the cord blood was 6.80 ± 0.12, and the cooling was initiated after the mean duration of 105.65 ± 113.30 minutes.

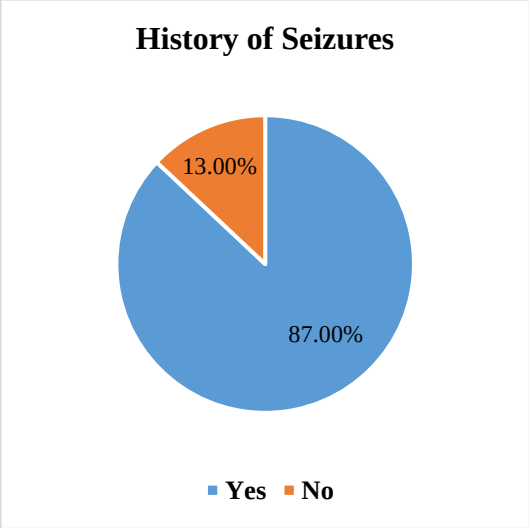

Fig 6. Distribution based on History of seizures among the study subjects

Figure 6 shows the Distribution based on History of seizures among the study subjects About 87.0% of neonates had history of seizures, and the mean time of occurrence of seizures among them was 16.10 ± 23.68 minutes.

Table 7: Distribution of the study subjects based on the clinical parameters

Clinical Parameters		Frequency(N)	Percentage(%)
Sinus Bradycardia	**Yes**	23	100.0%
	No	0	0.0%
Cardiac Arrhythmia	**Yes**	2	8.7%
	No	21	91.3%
Hypotension	**Yes**	14	60.9%
	No	9	39.1%
Persistent Pulmonary Hypertension	**Yes**	5	21.7%
	No	18	78.3%
Hemorrhage	**Yes**	10	43.5%
	No	13	56.5%
Altered level of Consciousness	**Yes**	20	87%
	No	3	13%
Mechanical Ventilation	**Yes**	15	65.2%
	No	8	34.8%

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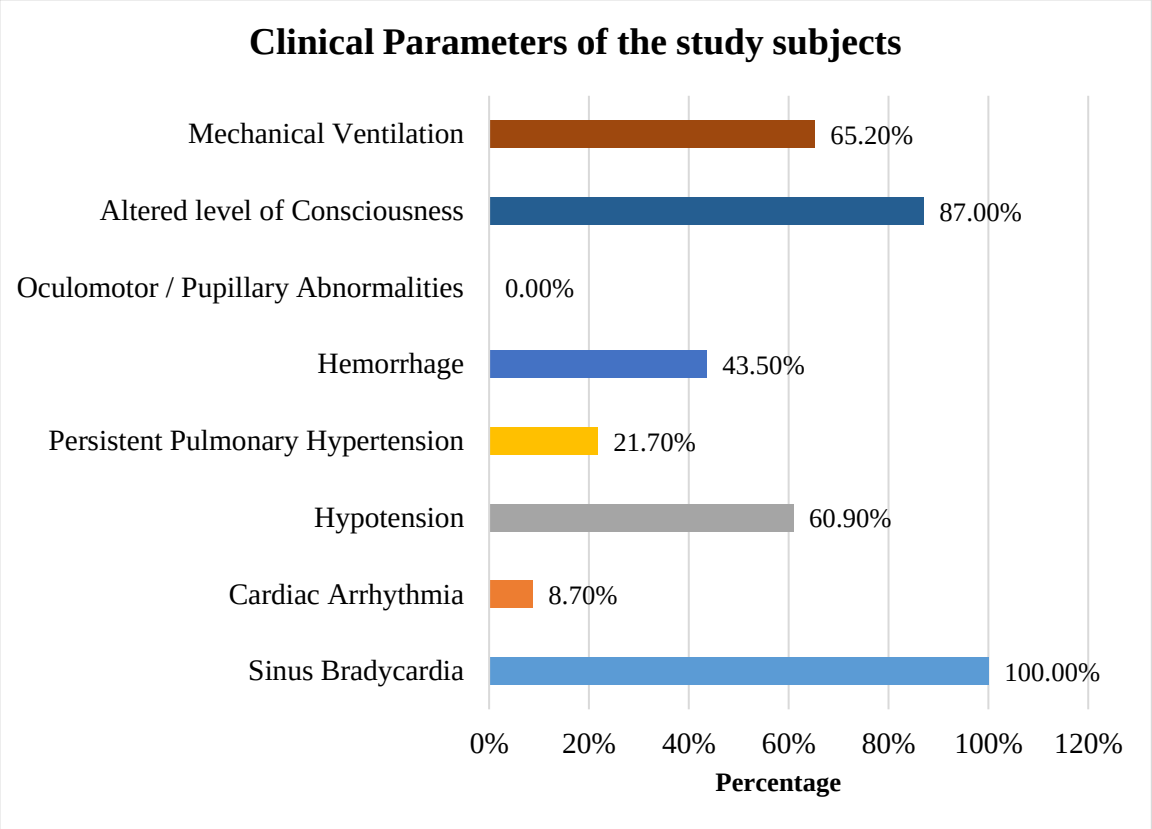

Fig 7. Distribution of the study subjects based on clinical parameters

Table 7 and Figure 7 shows the Distribution of the study subjects based on clinical parameters. Sinus bradycardia was the most common parameter observed in all neonates (100%). Cardiac arrhythmia was present in 2(8.7%), Hypotension in 14(60.9%), Persistent pulmonary hypertension in 5(21.7%), Haemorrhage in 10(43.5%), Altered level of consciousness in 20(87%), need for mechanical ventilation in 15(65.2%) neonates respectively.

Table 8: Laboratory parameters of the study subjects

Laboratory Parameters		Frequency (N)	Percentage (%)
Thrombocytopenia	**Present**	21	91.3%
	Absent	2	8.7%
Deranged Coagulation Profile	**Present**	16	69.6%
	Absent	7	30.4%
Altered Blood Glucose	**Hypoglycemia**	2	8.7%
	Hyperglycemia	7	30.4%
	Absent	14	60.9%
Electrolyte Abnormalities	**Hyponatremia**	8	34.8%
	Hypocalcemia	2	8.7%
	Hypokalemia	3	13.0%
	Hyperkalemia	2	8.7%
	Absent	8	34.8%
Acute Kidney Injury	**Present**	15	65.2%
	Absent	8	34.8%
Probable Sepsis	**Present**	19	82.6%
	Absent	4	17.4%
Culture Proven Sepsis	**Present**	5	21.7%
	Absent	18	78.3%

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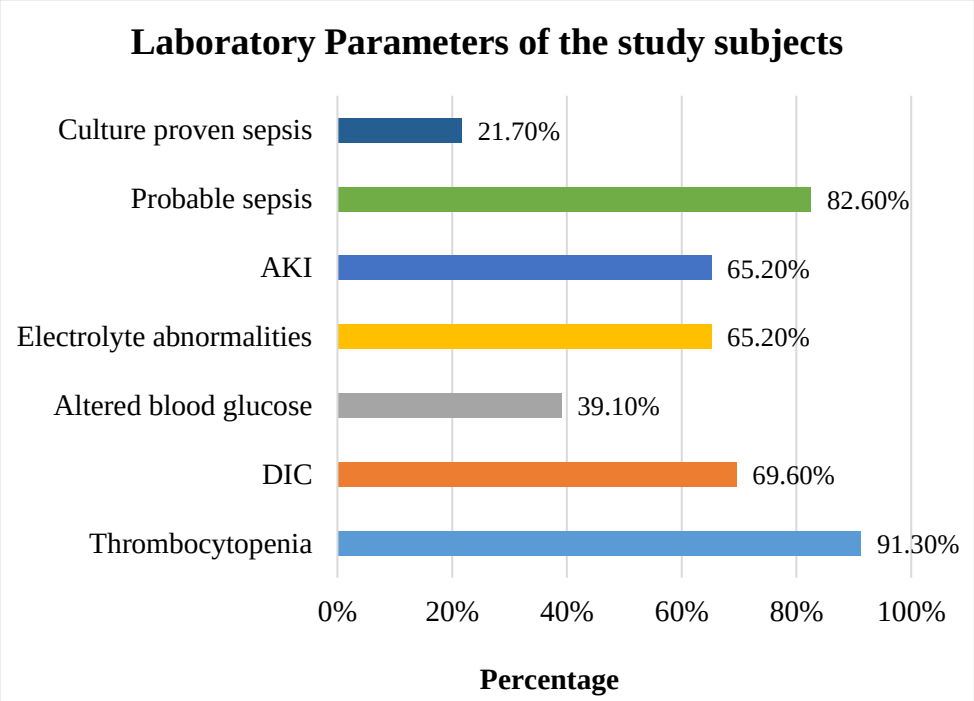

Fig 8. Distribution of the study subjects based on Laboratory parameters

Table 8 and Figure 8 shows the distribution of the study subjects based on Laboratory parameters. Thrombocytopenia was the most common parameter found in 21(91.3%) and DIC was present in 16(69.6%) neonates. Hyperglycemia was found in 7(30.4%), hypoglycemia in 2(8.7%) neonates. Hyponatremia was present in 8(34.8%), Hypocalcemia in 2(8.7%), Hypokalemia in 3(13%) and hyperkalemia in 2(8.7%) neonates. About 15(65.2%) neonates had suffered acute kidney injury, Probable sepsis was present in 19(82.6%) neonates and sepsis was culturally proven in 5(21.7%) neonates.

Table 9: Distribution of study subjects based on outcome

Characteristics		Frequency (N)	Percentage (%)
Gender	**Male**	14	60.9%
	Female	9	39.1%

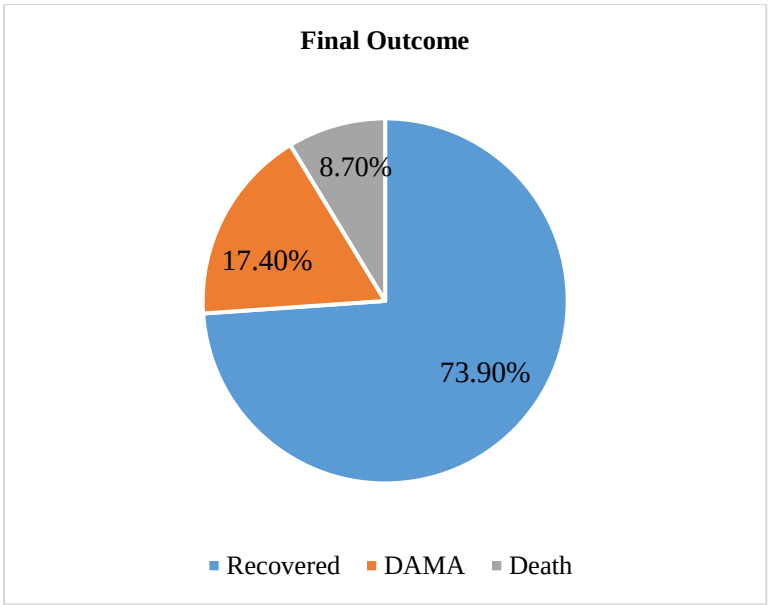

Fig 9. Distribution of the subjects based on Final outcome

Figure 9 shows Distribution of the subjects based on Final outcome. Overall, about 17(73.9%) neonates recovered after therapeutic cooling, while 2 cases could not be revived, and 4 cases got discharged against medical advice. The

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acute complications occurring in the neonates were determined based on the clinical and laboratory parameters which was compared with the outcome.

Table 10: Association between clinical parameters and final outcome

Clinical Parameters		Outcome				p-value #
		Death (N = 2)		Recovered (N = 17)		
		Frequency	Percentage	Frequency	Percentage	
Sinus Bradycardia	**Yes**	2	100.0%	17	100.0%	-
	No	0	0.0%	0	0.0%	
Cardiac Arrhythmia	**Yes**	1	50.0%	1	5.9%	0.050*
	No	1	50.0%	16	94.1%	
Hypotension	**Yes**	2	100.0%	9	52.9%	0.202
	No	0	0.0%	8	47.1%	
Persistent Pulmonary Hypertension	**Yes**	0	0.0%	4	23.5%	0.440
	No	2	100.0%	13	76.5%	
Hemorrhage	**Yes**	1	50.0%	6	35.3%	0.683
	No	1	50.0%	11	64.7%	
Oculomotor / Pupillary Abnormalities	**Yes**	0	0.0%	0	0.0%	-
	No	2	100.0%	17	100.0%	
Altered level of Consciousness	**Yes**	1	50.0%	15	88.2%	0.161
	No	1	50.0%	2	11.8%	
Mechanical Ventilation	**Yes**	2	100.0%	10	58.8%	0.253
	No	0	0.0%	7	41.2%	

Table 9 shows the Association between clinical parameters and final outcome. Sinus bradycardia was present in all neonates (100%). Cardiac arrhythmia was the only parameter which had statistically significant association with the outcome with a p value of o.o5.

Table 11: Association between laboratory parameters and final outcome

Laboratory Parameters		Outcome				p-value #
		Death (N = 2)		Recovered (N = 17)		
		Frequency	%	Frequency	%	
Thrombocytopenia	**Present**	1	50.0%	16	94.1%	0.050*
	Absent	1	50.0%	1	5.9%	
Deranged Coagulation Profile	**Present**	2	100.0%	10	58.8%	0.253
	Absent	0	0.0%	7	41.2%	
Altered Blood Glucose	**Hypoglycemia**	0	0.0%	1	5.9%	0.811
	Hyperglycemia	1	50.0%	5	29.4%	
	Absent	1	50.0%	11	64.7%	
Electrolyte Abnormalities	**Hyponatremia**	0	0.0%	7	41.2%	0.332
	Hypocalcaemia	0	0.0%	2	11.8%	
	Hypokalemia	0	0.0%	1	5.9%	
	Hyperkalemia	1	50.0%	1	5.9%	
	Absent	1	50.0%	6	35.3%	
Acute Kidney Injury	**Present**	1	50.0%	10	58.8%	0.811
	Absent	1	50.0%	7	41.2%	
Sepsis (Probable)	**Present**	2	100.0%	13	76.5%	0.440
	Absent	0	0.0%	4	23.5%	

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Sepsis (Culture Proven)	**Present**	1	50%	3	17.6%	0.050*
	Absent	1	50%	14	82.4%	
Seizures with >2 Anticonvulsants	**Present**	1	50.0%	7	41.2%	0.811
	Absent	1	50.0%	10	58.8%	

Table 10 shows the Association between laboratory parameters and final outcome. The study found statistically significant association of the final outcome only with respect to thrombocytopenia and culture proven sepsis with p values of 0.05.

DISCUSSION

In our study, 23 neonates were included with mean age of 76.52 ± 87.70 minutes. Majority were males (60.9%), and the mean birth weight was estimated to be 2.86 ± 0.42 kg, where about 13.0% were <2.5 kg. Caesarean section (65.2%) was the most common mode of delivery, while 8 neonates were out born (referred to our hospital after delivery). Necessary investigations were conducted in all therapeutic cooling neonates. About 65.2% had suffered acute kidney injury and sepsis was culturally proven in 5 children. About 47.8% of the neonates required more than or equal to 2 anticonvulsants. This study found statistically significant association of the final outcome only with respect to cardiac arrhythmia(P=0.05), culture proven sepsis(P=0.05) and thrombocytopenia(P=0.05).In a study by Bhagat I et al, most recent meta-analyses of the collective body cooling trials suggested that apart from thrombocytopenia and sinus bradycardia, therapeutic cooling (in the current recommended cooling range) in itself did not meaningfully affect the rate or the severity of multiple organ system complications commonly present in asphyxiated infants who received cooling compared with those who did not.[4] In a study by Aker.K et al, it was suggested that only thrombocytopenia and sinus bradycardia affected the neonates who received therapeutic cooling.[2] In a study by Brandt.J B, it was concluded that neoantes undergoing Therapeutic hypothermia showed earlier and higher increases in CRP levels when compared to normothermic controls. [9]

In a study by Nonato M et al, both head and whole-body cooling were demonstrated to have neuroprotective properties. [10] Another study by Hakobyan M et al, observed significant outcome in the majority of infants with perinatal asphyxia, TH, and early-onset sepsis. [11] Eriksen VR and his co-investigators proved that, asphyxiated new born infants had lower cardiac output previous to and during therapeutic hypothermia. The observed lower cardiac output may replicate a condensed metabolic rate in the asphyxiated new born infants. [12]

Our study showed that mortality was not more among birth asphyxia infants undergoing therapeutic cooling. Whilst in a study by Abate BB et al, it was showed that therapeutic hypothermia minimizes the risk of death in neonates with moderate to severe hypoxic-ischemic encephalopathy. Both selective head cooling and whole-body cooling were found effective in reducing the mortality of infants. [13] In our study therapeutic cooling caused AKI as a short-term difficulty but was not statistically momentous. In a study by Van wincoop M, TH in asphyxiated neonates condensed the frequency of AKI, an important risk factor for chronic kidney damage, and thus is possibly Reno protective. According to literature, no studies were found on the long-term effects of TH on myocardial function. [14]

Limitations of this study include less sample size due to lesser time period of the study and limited number of birth asphyxia cases during the study period. Only the acute complications were analyzed in this study and there is no long-term follow-up to assess the neurological outcome.

CONCLUSION

This study reveals that therapeutic hypothermia does not increase mortality in birth asphyxia infants. However, complications like sinus bradycardia, cardiac arrhythmia, thrombocytopenia requiring platelet transfusion, sepsis were commonly observed in neonates who received therapeutic cooling. Other complications like deranged coagulation profile, AKI, hypotension and electrolyte disturbances were also observed but were not statistically significant. But careful monitoring and strict adherence to therapeutic hypothermia protocol can prevent the occurrence of complications. Though mortality is low, morbidity and increased duration of hospital stay are seen with therapeutic cooling making the neonates more prone to sepsis. Complications like sepsis are negligible in western NICUs but same safety profile in our Indian ICUs is still a debate. But more clinical trials in NICUs of Low- and middle-income countries are required to support the evidence. Various studies have shown that selective head cooling was advantageous over whole body cooling in reducing the complications but due to logistics in low- and middle-income countries whole body cooling is used.

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CONFLICT OF INTEREST

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None

REFERENCES

1.Anne R. Hansen, Janet S.Soul.Perinatal asphyxia and Hypoxic-Ischemic Encephalopathy.Eric.C.Eichenwald. Cloherty and Stark's manual of Neonatal care,8th ed.Wolters kluwer:2016;791-812.

2.Aker K, Stoen R, Eikenes L, Martinez-Biarge M, Nakken I, Haberg AK et al. Therapeutic hypothermia for neonatal hypoxic-ischaemic encephalopathy in India (THIN study): a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2020; 105:405-11.

3. Datta V. Therapeutic Hypothermia for Birth Asphyxia in Neonates. Indian J Pediatr. 2017;84(3):219-26.

4.Bhagat I, Sarkar S. Multiple Organ Dysfunction During Therapeutic Cooling of Asphyxiated Infants. Neoreviews. 2019; 20:653-60.

5.Committee on fetus and newborn, American Academy of Pediatrics and Committee on obstetric practice, American College of Obstetrics and Gynecology. Use and abuse of the APGAR score.Pediatr 1996;98:141-2.

6. Yan F, Robert M, Li Y. Statistical methods and common problems in medical or biomedical science research. Int J Physiol Pathophysiol Pharmacol. 2017; 9:157-63.
7. Krousel-Wood MA, Chambers RB, Muntner P. Clinicians guide to statistics for medical practice and research: part I. Ochsner J. 2006;6(2):68-83.
8. Ali Z, Bhaskar SB. Basic statistical tools in research and data analysis. Indian J Anaesth. 2016; 60:662–9.
9.Brandt JB, Steiner S, Schlager G, Sadeghi K, Vargha R, Golej J et al. Necessity of early and continuous monitoring for possible infectious complications in children undergoing therapeutic hypothermia. Acta Paediatr 2021; 110:805-10.
10. Nonato M, Gheler L, Balestrieri JV, Audi M, Prandini M. Selective head cooling and whole body cooling as neuroprotective agents in severe perinatal asphyxia. Rev Assoc Med Bras.2019;65(8):1116-21.
11. Hakobyan M, Dijkman KP, Laroche S, Naulaers G, Rijken M, Steiner K et al. Outcome of Infants with Therapeutic Hypothermia after Perinatal Asphyxia and Early-Onset Sepsis. Neonatology. 2019;115(2):127-33.
12.Eriksen VR, Trautner S, Hahn GH, Greisen G. Lactate acidosis and cardiac output during initial therapeutic cooling in asphyxiated newborn infants. PLoS One. 2019 ;14(3):e0213537.
13. Abate BB, Bimerew M, Gebremichael B, Mengesha Kassie A, Kassaw M, Gebremeskel T et al. Effects of therapeutic hypothermia on death among asphyxiated neonates with hypoxic-ischemic encephalopathy: A systematic review and meta-analysis of randomized control trials. PLoS One. 2021;16(2):e0247229.
14. Van Wincoop M, de Bijl-Marcus K, Lilien M, van den Hoogen A, Groenendaal F. Effect of therapeutic hypothermia on renal and myocardial function in asphyxiated (near) term neonates: A systematic review and meta-analysis. PLoS One. 25;16(2):e0247403.