Effect of Therapeutic Hypothermia on Feeding Tolerance and Cerebral Oxygen Metabolism for Neonates with Hypoxic Ischemic Encephalopathy

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Abstract

Background: Therapeutic hypothermia is one of the main effective ways to support neuroprotection in neonates with hypoxic-ischemic encephalopathy. **Aim:** this study evaluated the effect of therapeutic hypothermia on feeding tolerance and cerebral oxygen metabolism for neonates with hypoxic ischemia encephalopathy. **Design:** A quasi-experimental design was utilized for conducting the current study (one group pre-post-test). **Setting:** This study was carried out in Neonatal Intensive Care Unit at Benha University Hospital which affiliated to the Ministry of Higher Education and Benha Specialized Pediatric Hospital which affiliated to the Ministry of Health and Population Specialized Medical Centers. **Subject:** A purposive sample of 45 neonates with hypoxic ischemia encephalopathy. **Data collection Tools:** The following five tools were utilized for data collection; **Tool I:** A Neonate's Medical data sheet: **Tool II:** Feeding Pattern of Neonates Assessment Sheet: **Tool III:** Neonates' Gastrointestinal Post Feeding Tolerance Assessment Sheet. **Tool IV:** Cerebral metabolic rate of oxygen consumption measurements. **Tool V:** Neonatal encephalopathy score. **Results:** The result of the present study revealed that there was a positive correlation and highly statistical significance between total neonatal body temperature and feeding tolerance and cerebral oxygen metabolism at pre and post therapeutic hypothermia intervention phases **Conclusion:** The study concluded that Therapeutic Hypothermia had highly statistical significance on feeding tolerance and cerebral oxygen metabolism for Neonates with Hypoxic Ischemia Encephalopathy. **Recommendation:** The therapeutic hypothermia study should be replicated on a larger random sample in different Neonatal Intensive Care Units, for the generalization of the obtained results.

Key Words: Therapeutic hypothermia, Feeding tolerance, Cerebral oxygen metabolism, Neonates, Hypoxic ischemic encephalopathy

Introduction:

Hypoxic-ischemic encephalopathy is One major form of brain injury brought on by inadequate oxygen delivery to the brain before or soon after birth is hypoxic-ischemic encephalopathy. The central nervous system is impacted. Hypoxic-ischemic encephalopathy can cause neurological or developmental issues in newborns. It frequently has an unexplained etiology **(Nationwide Children's Hospital, 2025), & (Branagan et al., 2024).**

The standard treatment for neonates with moderate to severe hypoxic-ischemic encephalopathy is therapeutic hypothermia, which involves cooling the brain several degrees below the baseline temperature. This can be achieved by cooling the infant to 33–34 °C for 72 hours within the first 6 hours of the hypoxic event, then gradually warming them up by 0.5 °C/h until the core temperature is maintained at 36.5–37.0 °C that can prevent or minimize permanent brain damage, and reduced neuroprotection **(Korf et al., 2023), & (Kyte, 2022).**

Feeding intolerance (FI) is a common disorder in newborns it refers to a difficulty of digesting enteral feedings and is associated by gastrointestinal disturbances such as reflux, distension in the abdomen, and an increase in gastric residuals. Moreover, an inability by the newborn to tolerate enteral nutrition **(Di Lorenzo, 2025).** Furthermore, therapeutic hypothermia has a vital and important effect on gastrointestinal functions as well as feeding tolerance in moderate-to-severe hypoxic-ischemic encephalopathy **(Costa et al., 2024).**

The rate at which oxygen is consumed is measured by cerebral oxygen metabolism. Cerebral oxygen metabolism is a critical aspect of brain function, reflecting how the brain consumes oxygen to produce energy for its activities. This process is essential for maintaining neuronal

activity, supporting cognitive functions, and responding to various physiological and pathological conditions **(Shetty et al., 2019).**

The nurse plays an essential role in the maintenance and rewarming stages of therapeutic hypothermia. The nurse in charge of the Neonatal Intensive Care Unit is adept at keeping an eye on chilled babies and searching for indications of recovery. It's critical that nurses understand how to treat hypoxic-ischemic encephalopathy with therapeutic hypothermia, evaluate neurological function, and determine the specific therapies required to maximize the neonate's chances of recovery **(Fang et al., 2023), & (Kelly, 2021).**

The nurse is responsible for monitoring the neonate's condition monitoring as blood pressure, oxygen saturation, and maintaining the target temperature to prevent brain damage and prevent medical complications. Nurses should make sure the infant is comfortable and responding well to treatment; the nurse must keep an eye on blood pressure, heart rate and rhythm, and ventilator alarms **(Blyth, 2019).**

Nurses who worked in Neonatal Intensive Care Units must be engaged in ongoing education and training in order to improve neonatal care and to understand the suitable and proactive maintenance that has been created. At the NICU, ongoing instruction is an active approach to premium nursing care (**Hockenberry, Wilson, & Rodgers, 2016**).

Significance of the study:

Neonatal hypoxic-ischemic encephalopathy is considered one of the most common causes of morbidity and mortality in neonates **(Ravichandran et al., 2020).** The incidence of hypoxic-ischemic encephalopathy is about 1 to 3 in 1000 live births in developed countries.

Worldwide,it causes more than half a million deaths each year **(Sharrow et al., 2024).** It is the third leading cause of death among neonates **(World Health Organization, 2015).**

In Egypt, it was stated that there were 25 neonatal deaths for every 1000 live births. According to this assessment, hypoxic ischemic encephalopathy is the second most common cause of newborn death, accounting for 18% of all neonatal deaths. In addition, about 16% of the newborns at the Neonatal Intensive Care Unit in certain Governorate had hypoxic-ischemic encephalopathy, so the urgent need for effective management **(Ali, 2018 & Abd Allah 2023).**

Therapeutic hypothermia is indicated for neonates have moderate to severe hypoxic ischemic encephalopathy. Furthermore, Supportive care is vital and critical to prevent extra harm from seizure activity, poor perfusion, electrolyte imbalance, abnormal glycemic control, and more advanced complication **(Zanelli, 2024).** Therefore, this study was conducted to evaluate the effect of therapeutic hypothermia on feeding tolerance and cerebral oxygen metabolism for neonates with hypoxic ischemia encephalopathy.

Aim of the Study:

The present study aimed to evaluate the effect of therapeutic hypothermia on feeding tolerance and cerebral oxygen metabolism for neonates with hypoxic ischemic encephalopathy through the following:

1. Assessing feeding tolerance and cerebral oxygen metabolism for neonates with hypoxic ischemic encephalopathy.
2. Preparing and implementing the steps of therapeutic hypothermia on neonates with hypoxic ischemic encephalopathy.

3. Evaluating the effect of therapeutic hypothermia on feeding tolerance and cerebral oxygen metabolism for neonates with hypoxic ischemic encephalopathy.

Research hypothesis:

Therapeutic hypothermia will improve feeding tolerance and cerebral oxygen metabolism for neonates with hypoxic ischemia encephalopathy

Subjects & Method:

Research design: A quasi-experimental one group pre-test, post-test design was utilized in this study.

Research setting: This study was carried out in Neonatal Intensive Care Units at Benha University Hospital which affiliated to the Ministry of Higher Education and Benha Specialized Pediatric Hospital which affiliated to the Ministry of Health and Population Specialized Medical Centers.

Subjects: A purposive sample of 45 neonates with hypoxic ischemic encephalopathy will be collected from the above-mentioned setting according to the **following Inclusion Criteria:**

- Gestational age ≥ 35 weeks

-Birth weight ≥ 1800 g

-Apgar scores ≤ 5 at 10 min of positive-pressure ventilation

- Cord pH is ≤ 7 in arterial, venous or capillary blood gas within 60 min after birth

-Neonates with moderate to severe hypoxic ischemic encephalopathy

Exclusion criteria:

- Neonates with gestational age < 35 weeks

- Neonates with severe intrauterine growth retardation with coagulopathy or severe head trauma, congenital infections, major malformations or inborn errors of metabolism, major congenital genetic abnormalities or intraventricular hemorrhage.

Data collection Tools: The following five tools were used for data collection; **Tool I: A neonate's**

medical data sheet: - It was designed by the researchers which comprises of two parts:

Part (1): Characteristics of the studied neonates: This includes gender, gestational age, birth weight, and current weight.

Part (2): Medical history of studied neonates: This includes medical diagnosis, Apgar score at 10 min of positive-pressure ventilation, mode of delivery, cerebral function monitoring and PH at birth.

Tool II: Neonates' feeding Pattern Assessment Sheet: This tool developed by researchers based on Sangers, et al., (2017), & Jebraieli, (2018): for assessing the feeding pattern for preterm neonates. It includes type of milk, mode of feeding, number and the amount of feeding per day.

Tool III: Neonates' Gastrointestinal Post Feeding Tolerance Assessment Sheet, which is adapted by the researchers from Sangers, et al., (2017), & Jebraieli, (2018) to assess the gastric residual volume of neonates. It includes amount of residual volume, color of residual volume, abdominal distention and vomiting.

Tool IV: Cerebral metabolic rate of oxygen consumption (CMRO2) measurements: Which adapted from **Brown et al, (2003).** It was determined from measurement hemoglobin oxygen saturation (SaO2) and cerebral blood flow index values. And Magnetic Resonance Imaging (MRI) adapted from **Barkovich et al, (1998).** Classifying the findings according to the grading system was available of neonate to assess the severity of brain injury, Magnetic Resonance Imaging scores significantly increased with increased severity of encephalopathy.

Tool V: Neonatal encephalopathy (NE) score:

The researchers adopted from (**Mrelashvili et al., 2020).** Modified

Sarnat Score test to determine NE scores.

Scoring system: It contains six categories: autonomic system activity, tone, posture, spontaneous activity, state of consciousness, and basic reflexes. The score varied from 0 to 18, with each category receiving a value of 0 for normal, 1 for mild, 2 for moderate, or 3 for severe.

- Total neonatal encephalopathy Score = 0–18

Total Scoring	system of Encephalopathy
1–6	Mild
7–12	Moderate
13–18	Severe

II-Administrative design:

Prior to collection of data researchers submitted and obtained an official letter from the dean of Faculty of nursing Benha University outlining the study goals and data collecting procedures, the written formal consent from director of each setting was given for conducting the study.

II. Operational design:

The operational design included: preparatory phase, content validity, reliability of tool, pilot study and field work.

The preparatory phase

This phase involved reviewing relevant literature, various studies, and theoretical knowledge of various aspects of the study. Textbooks, evidence-based articles, internet, periodicals, and journals were also used in order to develop tools and become familiar with the various study aspects of the research problems.

Tools validity:

Tools validity was checked by a jury of three experts (professors) of Pediatric Nursing in the Faculty of Nursing, Benha University for checking the content validity of the instruments and judging its clarity, simplicity, relevance,

comprehensiveness and accuracy. All of comments were considered. Tool items were rephrased. The tools were graded as valid according to the point of view of jury experts.

Reliability:

The researchers used tool reliability to examine the internal consistency of the instruments by administering the same instrument to the same people in comparable circumstances. The Cronbach's alpha coefficient test was used to evaluate the internal consistency reliability of all the tool items. The results showed that the neonatal encephalopathy (NE) score was 0.77, the cerebral metabolic rate of oxygen consumption was 0.82, the neonates' feeding pattern assessment sheet was 0.79, and the neonates' gastrointestinal post-feeding tolerance assessment sheet was 0.87.

Ethical considerations:

Approval of ethics granted from the Scientific Research Ethical Committee of Faculty of Nursing, Benha University (ethical approval reference number is REC-PN-P 61 on 5 November 2024, an official approval was obtained from directors of the NICU at Benha University Hospital and Benha Specialized Pediatric hospital. Informed consent prior to data collection obtained from the neonates' parents after being assured about all obtained data used for research purpose only and the study steps are safe and harmless. Additionally, neonates' parents informed that they are allowed to withdraw from the study at any time. The confidentiality of the data collected as well as results were well secured.

Pilot study:

Pilot study was conducted on 10% of the total sample size (5 neonates) to test the applicability and validity of the study tools and to determine how long it would take to fulfill the questionnaire. The pilot sample included the subjects in the study because there were no significant

modifications carried out on the study tools.

Field work:

Study was carried out on the beginning of November 2024 and finished at the end of March 2025 lasting 5 months. The researchers visited the previously mentioned setting three days/week (Sundays, Tuesdays, and Thursdays) from 9 AM to 12 PM for collecting data by using preceding tools. The researcher interviewed the neonates' parents individually and explained the nature and purpose of the study in order to take parents' consent with emphasizing on safety and usefulness of study aim. Each interview took time from 15 to 30 minutes.

-The researchers started data collection by assessing socio demographic data, medical data through neonatal characteristics using tool I. In addition, assessing neonates feeding tolerance using tool II, III, assessing cerebral oxygen rate using tool IV, and neonatal encephalopathy (NE) score using tool V.

Phases of Therapeutic Hypothermia

• Induction phase:

- The researcher starts cooling within 6 hours of birth and continues for 72 hours.
- Apply cool pack to the back of the neck and head and across the torso if required.
- Cool pack temperature started at 10 °C (acquire from the fridge, never the freezer).
- Cover cool pack with appropriate cotton cover
- Observe the contacted skin with cool pack every 15 minutes and document any observation till reach the targeted core temperature at 33.50°C, it took about 30 minutes. Temperature was checked every 15 min at the first hour and then each hour.
- Stop active warming by stopping the heater, opening port holes and

keeping the baby unclothed from a diaper.

• **Maintenance phase: is** characterized by maintenance of core temperature between range of **33-34°C** for 72 hours. Turning the heater on if the temperature is less than 33.5 °C and continuing closely to monitor the temperature.

• **Rewarming phase:**

Maintained rewarming gradually started after 72 h of hypothermia at 0.50°C per hour (6 hours) from 33.50°C to 36.50°C. Continuous monitoring of vitals as blood pressure, heart rate, respiratory rate and SpO2. Glucose monitoring was done every 8 hours.

Feeding was started at minimal volumes (10-20 mL/kg/day) administered every three hours as an intermittent bolus via an orogastric or nasogastric tube. During therapeutic hypothermia, the total intravenous fluid volume was kept between 50 and 60 milliliters per kilogram per day.

Commencing enteral feeds in infants during therapeutic hypothermia should be considered on an individualized basis, considering the whole clinical state.

Supportive Management

Monitoring: through cooling and rewarming period should include:

Continuous temperature, heart rate, respiration rate and blood pressure monitoring in addition to oxygen saturation

Evaluation Phase:

After the application of the therapeutic hypothermia phases, the feeding tolerance and cerebral oxygen metabolism for neonates with hypoxic ischemia encephalopathy were evaluated immediately. The post-test was done using the same pretest tools for data collection.

IV- Statistical Design:

The collected data was organized, tabulated and analyzed statistically

by Statistical Package for Social Science (SPSS) version 21 for windows, running on IBM compatible computer. Descriptive statistics were applied (e.g. Number, percentages, mean and standard deviation). Test of significance, Chi-square test (χ^2) this test used to measure significant of qualitative variables, paired t test used to measure significant of quantitative variables and correlation coefficient (r) used for quantitative variables that were normally distributed or when one of the variables is qualitative. These tests were applied to test the study hypothesis. Reliability of the study tools was done using Cronbach's Alpha. A highly significant level value was considered when $p < 0.001$, a significant level value was considered when $p < 0.05$ and no statistical significance difference considered when $p > 0.05$.

Results:

Table (1): Shows that, majority (80.0%) of studied neonates were gestational age ranged from 37 – <39 week with mean ± SD 37.97±1.15 week, concerning gender, that more than two thirds (73.3%) of them were male. Regarding birth weight less than half (48.9%) of them ranged from3000- ≤3500 g with mean ± SD 2760.00±476.44 g and regarding current weight less than half (46.7%) of them ranged from3000- ≤3500 g with mean ± SD 3111.11±467.69 g.

Table (2): Portrays that, more than three quarters (75.5%) of studied neonates had score <5 Apgar score at 10 min of positive-pressure ventilation with Mean ± SD 4.88± 1.38. Regarding mode of delivery, more than two thirds (73.3%) of them were delivered by cesarean section, while majority (84.4%) of them had birth asphyxia. Concerning Hypoxic-ischemic encephalopathy more than half (51.1%) of neonate diagnosed moderate Hypoxic-ischemic encephalopathy, also more than half

(57.8%) of them had moderately abnormal cerebral function monitoring. Regarding pH at birth of neonate had Mean ± SD 7.04 ± 0.015 and body temperature at admission Mean ± SD 36.2± 0.3 ◦c.

Table (3): Reveals that, more than three quarters (75.6%,80.0 %,68.9 , 86.9%) of studied neonates were feeding with formula milk at Pre, first, second and third day of therapeutic hypothermia respectively, while more than half (62.2%) of them were feeding with Human milk at post of therapeutic hypothermia. Regarding feeding methods, more than half (64.4%) of them were feeding by continuous tube feeding at Pre therapeutic hypothermia, while (62.2%,57.8 %, 46.7%) were feeding by bolus tube feeding at first, second and third day of therapeutic hypothermia respectively, and less than half (46.7%) feeding by bottle at post of therapeutic hypothermia. Moreover, there was highly statistically significant difference in all items of neonates according to their feeding pattern at pre, first, second and third day and post therapeutic hypothermia intervention phases (p<0 .000).

Table (4): Shows that, majority (82.2%, 84.5%, 64.5%) of neonates had abdominal distention at pre, first, second day of therapeutic hypothermia respectively, while more than half (55.5%&95.6%) of them did not have abdominal distention on the third day and post therapeutic hypothermia respectively. Moreover, there was highly statistically significant difference in all items of neonates according to their feeding tolerance at pre, first, second and third day and post therapeutic hypothermia intervention phases (p<0 .000).

Figure (1): Illustrates that more than three quarters (.755%) of studied neonates hadn’t total score of feeding tolerance at pre therapeutic hypothermia intervention. While improvement to (86.8%) had total

score of feeding tolerance at post therapeutic hypothermia intervention.

Table (5): Reveals that less than half (48.9%,44.4%) of studied neonates had Lethargic at pre and first therapeutic hypothermia intervention phases respectively, while about one third (33.3%) of them had responds to minimal stimuli at second therapeutic hypothermia intervention and (46.7% &62.2%) of them were improved to alert, responsive at post therapeutic hypothermia intervention respectively. Moreover, there was highly statistically significant difference in all items of neonates according to their Neonatal encephalopathy (NE) score at pre, first, second and third day and post therapeutic hypothermia intervention phases (p<0 .000).

Figure (2): Clarifies that, more than half (51.1%) of studied neonates had total score of moderate Hypoxic Ischemic Encephalopathy at pre therapeutic hypothermia intervention, while improvement to (82.7%) had total score of mild Hypoxic Ischemic Encephalopathy at post therapeutic hypothermia intervention.

Table 6: Reflects that there was highly statistically significant difference between magnetic resonance image (MRI) scores and severity of Hypoxic Ischemic Encephalopathy (HIE) at pre and post therapeutic hypothermia intervention phases (p<0 .000).

Table (7): Portrays that, score and SD of the studied neonatal cerebral metabolic rate of oxygen consumption measurements, It was found that, improvement the mean of oxygen saturation of neonatal (88.25±1.55, 92.87±1.43, 95.37±0.60, 97.17±0.44,& 99.66±0.56) at pre, first, second and third day and post therapeutic hypothermia intervention phases respectively, there was highly statistically significant difference in

oxygen saturation at pre, first, second and third day and post therapeutic hypothermia intervention phases (p<0 .000).

Table (8): Reveals that, there was a positive correlation and highly statistical significance between total neonatal body temperature and feeding tolerance and cerebral oxygen metabolism at pre and post therapeutic hypothermia intervention phases (p<0 .000).

Table (9): Presents that, there was highly statistically significant relation between neonatal total score severity of hypoxic ischemic encephalopathy and their gestational age and birth weight at pre and post therapeutic hypothermia intervention phases (p<0 .000).

Table (1): Percentage Distribution of the studied neonates according to their characteristics (n= 45)

Personal characteristics	No.	%
Gestational age /weeks		
35 - <37 week	4	8.9
37 – <39 week	36	80.0
39- ≤ 42 weeks	5	11.1
Mean ±SD 37.97±1.15 week		
Gender		
Male	33	**73.3**
Female	12	26.7
Birth weight, g		
1800-<2000	4	8.9
2000-<2500	7	15.5
2500-<3000	12	26.7
3000- ≤3500	22	**48.9**
Mean ± SD 2760.00±476.44 g		
Current weight/ g		
2000-<2500	6	13.3
2500-<3000	10	22.2
3000-<3500	21	**46.7**
3500- ≤4000	8	17.8
Mean ±SD 3111.11±467.69 **g**		

Table (2): Percentage Distribution of the studied neonates according to their medical history (n=45)

Medical history	No.	%
Apgar score at 10 min of positive-pressure ventilation		
< 5	34	**75.5**
5-7	8	17.8
7-10	3	6.7
Mean ± SD 4.88± 1.38		
Mode of delivery		
Normal	12	26.7
Cesarean Section	33	**73.3**
Birth asphyxia		
Yes	38	**84.4**
No	7	15.6
Hypoxic-ischemic encephalopathy, n		
Mild	5	11.1
Moderate	23	**51.1**
Sever	17	37.8
Cerebral function monitoring		
Normal	2	4.4
Moderately abnormal	26	**57.8**
Sever abnormal	17	37.8
pH at birth Mean ± SD 7.04 ± 0.015		
Body temperature at admission Mean ± SD 36.2± 0.3 c^o		
Temperature during therapeutic hypothermia Mean ± SD 33.5 ± 0.3 c^o		

Table (3): Percentage Distribution of the studied neonates according to their feeding pattern pre, first, second and third day and post therapeutic hypothermia intervention phases (n=45)

Feeding Pattern	Pre-therapeutic hypothermia	First day during therapeutic hypothermia	Second day during therapeutic hypothermia	Third day during therapeutic hypothermia	Post therapeutic hypothermia	X2 FET	P value
	%	%	%	%	%		
Type of milk							
Human milk	24.4	20.0	31.1	31.1	**62.2**	38.65	0.000
Formula milk	**75.6**	**80.0**	**68.9**	**86.9**	37.8		
Feeding method							
Bottle	6.7	8.9	17.8	31.1	**46.7**	93.55	0.000
Bolus tube feeding	28.9	**62.2**	**57.8**	**46.7**	20.0		
Continuous tube feeding	**64.4**	28.9	24.4	22.2	33.3		
Number of feeding/day							
3	66.7	48.9	44.4	37.8	11.1	61.64	. 0.000
4	28.9	40.0	40.0	40.0	46.7		
5	4.4	11.1	15.6	22.2	42.2		
Feeding volume (ml\ day)							
10	71.2	57.8	40.0	24.4	8.8	84.24	0.000
10-20	20.0	33.4	44.5	42.3	62.3		
20-30	8.8	8.8	15.5	33.3	28.9		

Table (4): Percentage Distribution of the studied neonates according to their feeding tolerance pre, first, second and third day and post therapeutic hypothermia intervention phases (n=45)

Feeding Tolerance	Pre-therapeutic hypothermia	First day during therapeutic hypothermia	Second day during therapeutic hypothermia	Third day during therapeutic hypothermia	Post therapeutic hypothermia	X^2 FET	P value
	%	%	%	%	%		
Amount of residual Volume							
0 -<3 cm.	40.0	40.0	44.5	33.3	82.2	87.46	0.000
3-<6 cm.	42.2	40.0	40.0	35.6	11.1		
6-≤9 cm.	17.8	20.0	15.5	31.1	6.7		
Color of residual volume							
Unclear	84.4	75.6	62.2	37.8	17.8	89.18	0.000
Clear	15.6	24.4	37.8	62.2	82.2		
Signs of feeding Tolerance							
Abdominal distention							
Yes	**82.2**	**84.5**	**64.5**	44.5	4.4	84.21	0.000
No	17.8	15.5	35.5	**55.5**	**95.6**		
Vomiting							
Yes	84.5	80.0	71.1	48.9	8.8	74.23	0.000
No	15.5	20.0	28.9	51.1	91.2		

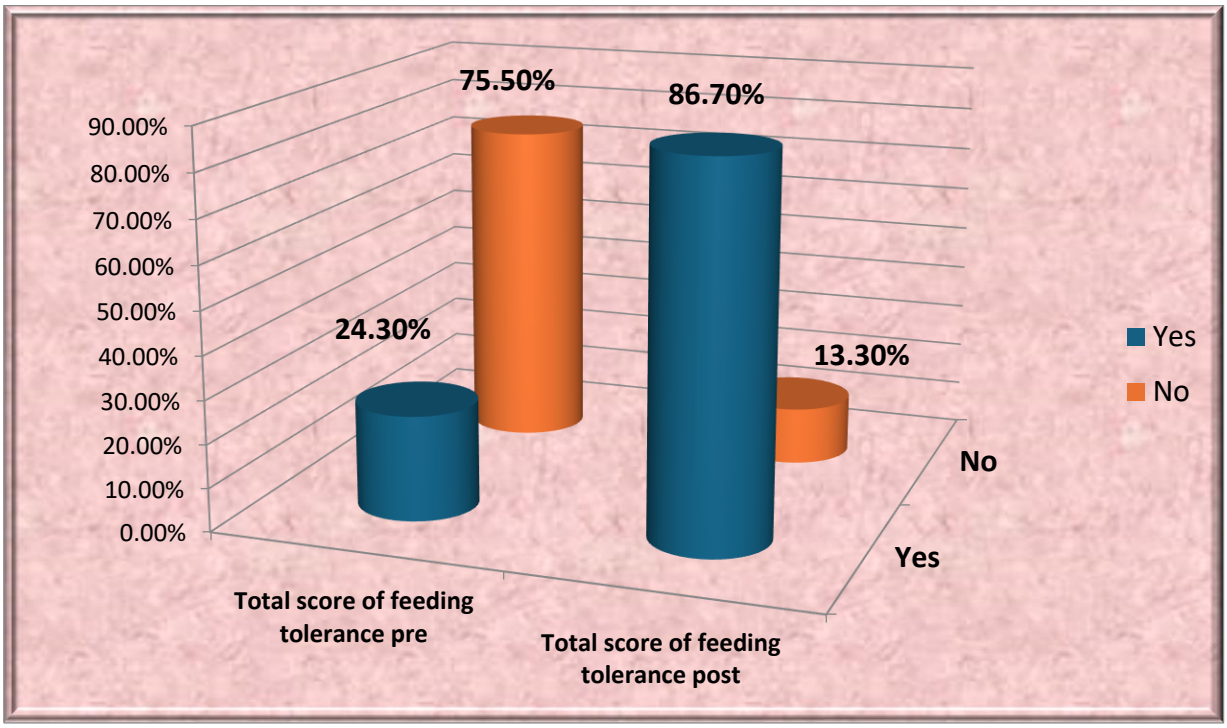

Figure (1): Distribution of the studied neonates regarding their total score of feeding tolerance pre and post therapeutic hypothermia intervention phases (n=45)

Table (5): Percentage Distribution of the studied neonates according to their neonatal encephalopathy (NE) score at pre, first, second and third day and post therapeutic hypothermia intervention phases (n=45)

Neonatal Encephalopathy	Pre-therapeutic hypothermia	First day during therapeutic hypothermia	Second day during therapeutic hypothermia	Third day during therapeutic hypothermia	Post therapeutic hypothermia	X2 FET	P value
	%	%	%	%	%		
Level of consciousness							
Alert, responsive	11.1	15.6	26.7	**46.7**	**62.2**	77.18	0.000
Responds to minimal stimuli	15.6	24.4	**33.3**	28.9	28.9		
Lethargic	**48.9**	**44.4**	31.1	20.0	4.4		
Stupor or coma	24.4	15.6	8.9	4.4	4.4		
Suck reflex							
Absent	35.6	24.4	13.3	8.9	2.2	80.20	0.000
Weak	57.8	64.4	53.4	31.1	28.9		
Strong	6.7	11.1	33.3	60.0	68.9		
Moro reflex							
Absent	42.2	26.6	15.6	11.1	4.4	93.23	0.000
Weak	46.7	57.8	51.1	42.2	17.8		
Strong	11.1	15.6	33.3	46.7	77.8		
Tonic neck reflex							
Absent	37.8	28.9	20.0	6.6	4.4	88.98	0.000
Weak	53.3	51.1	57.8	46.7	13.3		
Strong	8.9	20.0	22.2	46.7	82.3		

Continue Table (5): Percentage distribution of the studied neonates according to their neonatal encephalopathy (NE) score at pre, first, second and third day and post therapeutic hypothermia intervention phases (n=45)

Neonatal Encephalopathy	Pre-therapeutic hypothermia	First day during therapeutic hypothermia	Second day during therapeutic hypothermia	Third day during therapeutic hypothermia	Post therapeutic hypothermia	X^2 FET	P value
	%	%	%	%	%		
Autonomic Nervous System: Pupils							
Reactive	8.9	22.2	35.6	48.9	80.4	86.43	0.000
Dilated pupil.	24.4	24.4	22.2	31.1	13.3		
Constricted pupil.	42.3	35.6	28.9	11.1	2.3		
Nonreactive	24.4	17.8	13.3	8.9	4.0		
Heart rate							
Normal	8.9	17.8	28.9	53.3	71.2	61.80	0.000
Tachycardia.	22.2	35.6	26.7	20.0	11.1		
Bradycardia	26.7	17.8	26.7	17.8	13.3		
Variable	42.2	28.9	17.7	8.9	4.4		
Respiratory rate							
Regular	6.7	15.6	22.2	46.7	62.2	78.45	0.000
Tachypnea	22.2	22.2	26.7	11.1	13.3		
Periodic breathing	24.4	28.9	26.7	28.9	17.8		
Apnea	46.7	33.3	24.4	13.3	6.7		
Seizure							
None	11.1	24.4	37.8	55.6	73.4	82.14	0.000
Common; focal or multifocal	57.8	37.8	26.7	8.9	4.4		
Uncommon (excluding decerebration)	31.1	37.8	35.5	35.5	22.2		

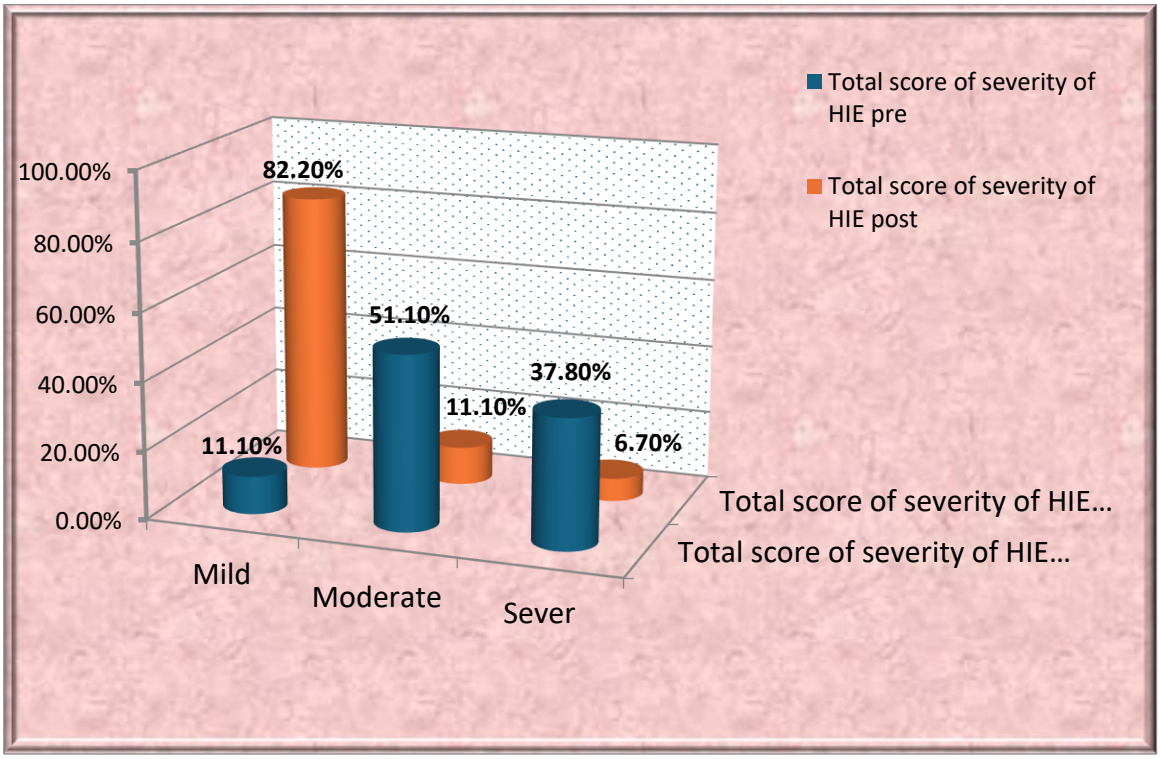

Figure (2): Distribution of the studied neonates according to their total score of severity of Hypoxic Ischemic Encephalopathy at pre and post therapeutic hypothermia intervention phases(n=45).

Table 6: Percentage distribution of the studied neonates regarding to their cerebral metabolic according to Magnetic Resonance Image (MRI) scores and severity of Hypoxic Ischemic Encephalopathy (HIE) at pre and post therapeutic hypothermia intervention phases (n=45)

Items	Severity of HIE Pre- therapeutic hypothermia (n= 45)			Severity of HIE Post - therapeutic hypothermia (n= 45)			X2 FET	P value
MRI scores	Mild n=5	Moderate n=23	Sever n=17	Mild n=37	Moderate n=5	Sever n=3		
Normal n (%)	2 (40.0)	3 (13.1)	1 (5.8)	**30 (81.0)**	2 (40.0)	2 (66.6)	55.45	0.000
Mild n (%)	1 (20.0)	5 (21.7)	2 (11.8)	4(10.8)	2 (40.0)	1 (33.4)	67.23	0.000
Moderate n (%)	1 (20.0)	**11 (47.8)**	5 (29.5)	3 (8.2)	1 (20.0)	0 (0.0)	49.66	0.000
Sever n (%)	1 (20.0)	4 (17.4)	9 (52.9)	0 (0.0)	0 (0.0)	0 (0.0)	53.45	0.000

Table (7): Mean score of the studied neonate according to cerebral metabolic rate of oxygen consumption (CMRO2) measurements at pre, first, second and third day and post therapeutic hypothermia intervention phases(n=45)

Items	Pre-therapeutic hypothermia	First day during therapeutic hypothermia	Second day during therapeutic hypothermia	Third day during therapeutic hypothermia	Post therapeutic hypothermia	Paired t test (pre-post)	P value
Oxygen Saturation	88.25±1.55	92.87±1.43	95.37±0.60	97.17±0.44	99.66±0.56	**85.66**	**0.000**
Body temperature	36.2± 0.3 c^o	33.5 ± 0.3 c^o	33.5 ± 0.3 c^o	33.5 ± 0.3 c^o	37.2±0.4 c^o	**54.23**	**0.000**

Table (8): Correlation between studied neonatal body temperature and feeding tolerance and cerebral oxygen metabolism at pre and post therapeutic hypothermia intervention phases (no=45)

Total scores	Pearson correlation coefficient			
	Pre- therapeutic hypothermia		Post- therapeutic hypothermia	
	r	P-value	r	P-value
Body temperature -hypoxic ischemic encephalopathy	0.544	0.000	0.747	0.000
Body temperature - feeding tolerance	0.604	0.000	0.869	0.000
Body temperature - cerebral oxygen metabolism	0.436	0.000	0.528	0.000
Feeding tolerance -hypoxic ischemic encephalopathy -	0.391	0.000	0.469	0.000
Cerebral oxygen metabolism -hypoxic ischemic encephalopathy	0.201	0.000	0.676	0.000

Table (9): Relation between the studied neonatal total score severity of Hypoxic Ischemic Encephalopathy (HIE) and their personal characteristics at pre and post therapeutic hypothermia intervention phases (n= 45).

Personal characteristics	Severity of HIE Pre- therapeutic hypothermia (n= 45)						X^2	p-value	Severity of HIE Post - therapeutic hypothermia(n= 45)						X^2	p-value
	Mild n=5		Moderate n=23		Sever n=17				Mild n=37		Moderate n=5		Sever n=3			
	No	%	No	%	No	%			No	%	No	%	No	%		
Gestational age/weeks							63.88	0.000							31.20	0.000
35 - <37 week (n=4)	1	20.0	1	4.3	2	11.9			2	5.4	1	20.0	1	33.4		
37 – <39 week (n=36)	3	60.0	19	82.6	14	82.3			33	89.2	3	60.0	0	0.0		
39- ≤42 week (n=5)	1	20.0	3	13.1	1	5.8			2	5.4	1	20.0	2	66.6		
Birth weight, g							34.20	0.000							48.55	0.000
1800-<2000 (n=4)	1	20.0	2	8.6	1	5.8			1	2.7	2	40.0	1	33.3		
2000-<2500 (n=7)	1	20.0	2	8.6	4	23.6			5	13.5	1	20.0	1	33.3		
2500-<3000 (n=12)	1	20.0	8	34.8	3	17.7			10	27.1	1	20.0	1	33.4		
3000- ≤3500 (n=22)	2	40.0	11	47.8	9	52.9			21	56.7	1	20.0	0	0.0		

Discussion

Therapeutic hypothermia is currently the only evidence-based neuroprotective intervention shown to significantly improve outcomes in full-term and near-term neonates with moderate to severe hypoxic-ischemic encephalopathy **(Shah et al., 2025).** Early therapeutic hypothermia was recommended to provide better neuroprotection compared to delayed treatment **Korf et al., (2023).**

Regarding the mode of delivery, this study showed that the majority of the studied neonates delivered by caesareans section. This was consistent with the study by **Sayed et al., (2024).** " Caregivers, Awareness of Neonatal Hypoxic Ischemic Encephalopathy and Subsequent Infant Development " who reported that most neonates were delivered by caesareans section. This indicates that caesareans section considers one of the most predisposing factors of hypoxic ischemic encephalopathy.

In relation to neonates' Apgar score, the result of the present study revealed that two third of the studied neonates had Apgar score less than 5 at 10 min of positive-pressure ventilation. This result was similar with the study conducted by **Martinovski et al., (2025).** Enteral Feeding in Neonatal Hypoxic-Ischemic Encephalopathy " Who mentioned that Apgar scores were less than 5 at 5 minutes.

As regards to, type of milk the result revealed that, more than three quarters of studied neonate were feeding with formula milk pre therapeutic hypothermia, while more than half of them were feeding with human milk at post of therapeutic hypothermia. This result similar to the result of **Abd El-Halim (2022)** "Recording of Complications of Treatment of Hypoxic Ischemic Neonates by

Passive Whole-Body Cooling: A Study in Neonatal Intensive Care Unit of Mataria Teaching Hospital" who mentioned that neonates feeding improved which feeding by breast feeding after therapeutic hypothermia. This indicated that therapeutic hypothermia effects on quality and quantity of feeding.

In addition, **Hu et al., (2022)** " Early versus delayed enteral nutrition for neonatal hypoxic-ischemic encephalopathy undergoing therapeutic hypothermia: a randomized controlled trial" who mentioned that before therapeutic hypothermia the neonates have feeding by tube feeding while after therapeutic hypothermia most of neonates have breastfeeding.

Regarding feeding tolerance the result of the present study showed that there was highly statistically significant difference in all items of neonates according to their feeding tolerance at pre, first, second and third day and post therapeutic hypothermia intervention phases with finding was in consistent with **Samaai et al., (2025).** Who found that feeding tolerance of neonates improved after therapeutic hypothermia which improves gastrointestinal function and disturbance as abdominal distention, and vomiting.

Concerning, heart rate the present study showed that heart rate before therapeutic hypothermia was abnormal, about less than half of them and after therapeutic hypothermia was at a normal level of about two third of them. This result consistent with **Wagdy et al., (2023).** " The Immediate Impact of Therapeutic Hypothermia on Cardiac Function of Neonates with Hypoxic Ischemic Encephalopathy" who reported that heart rate level improved after therapeutic hypothermia than before therapeutic hypothermia.

The current study illustrated that less than half of studied neonate had Lethargic at pre and first therapeutic hypothermia intervention phases respectively, while about one third of them had responds to minimal stimuli at second therapeutic hypothermia intervention and less than half of them were improve to alert, responsive at third day of therapeutic hypothermia intervention and more than half of them were improve to alert, responsive at post of therapeutic hypothermia intervention . This finding agreed with **Montaldo et al., (2022)** who study showed that the incidence of brain injury in the therapeutic hypothermia group) was significantly lower than that in the non- therapeutic hypothermia group, indicating that therapeutic hypothermia is effective in treating mild hypoxic ischemic encephalopathy neonates and found a higher incidence of brain injury and adverse neurological outcomes in mild hypoxic ischemic encephalopathy neonates with the progression of encephalopathy.

In addition, the present study showed that reflexes as Moro, and sucking were weak or absent more than one third of the studied neonates pre therapeutic hypothermia while more than two thirds of them post therapeutic hypothermia were gradually increased to become strong. This finding was agreed with **Kruger et al., (2017).** " Breastfeeding and swallowing in a neonate with mild hypoxic-ischemic encephalopathy" Who found that sucking and Moro reflexes were absent in first admission of neonates while after receiving therapeutic hypothermia changed to strong.

Regarding Magnetic Resonance Image (MRI) scores, the result of the present study found that there was highly statistically significant difference between Magnetic

Resonance Image (MRI) scores and severity of hypoxic-ischemic encephalopathy at pre and post therapeutic hypothermia intervention phases. This result agreed with **Guarnera et al., (2023).** " Predictive Value of MRI in Hypoxic-Ischemic Encephalopathy Treated with Therapeutic Hypothermia" who reported that there were some significant correlations between Magnetic Resonance Image (MRI) and neurodevelopmental outcomes of neonates.

There was highly statistically significant difference in oxygen saturation at pre, first, second and third day and post therapeutic hypothermia intervention phases. This finding is supported by **Shetty et al., (2019)** in study entitled "Cerebral oxygen metabolism in neonatal hypoxic ischemic encephalopathy during and after therapeutic hypothermia" Who found that cerebral blood volume (CBV) and hemoglobin oxygen saturation (SO2) were significantly higher in neonates with hypoxic-ischemic encephalopathy during therapeutic hypothermia compared with age-matched control neonates.

Undoubtedly, therapeutic hypothermia not only improves survival and neurodevelopment after neonatal hypoxic-ischemic encephalopathy but also favorably influences oxygen metabolism. By lowering whole-body and cerebral metabolic demand, therapeutic hypothermia reduces cerebral oxygen consumption ($CMRO_2$) in a temperature-dependent manner about 14% per °C stabilizing oxygen extraction and perfusion during the critical early days, which correlates with better downstream neurodevelopmental outcomes **Jiang et al., (2025).**

The finding of the study revealed that there was a positive correlation and

highly statistical significance between total neonatal body temperature and feeding tolerance at pre and post therapeutic hypothermia intervention phases. This finding was consistent with finding of **Sakhuja et al., (2019).** "Gastrointestinal hemodynamic changes during therapeutic hypothermia and after rewarming in neonatal hypoxic-Ischemic encephalopathy" who reported that after rewarming the neonatal intestine work more effectively. This indicated that therapeutic hypothermia had positive effect on gastric function that helps neonates in feeding tolerance.

The finding of the present study revealed that more than half of studied neonate had total score of moderate hypoxic-ischemic encephalopathy at pre therapeutic hypothermia intervention, while improvement to more than two thirds had total score of mild hypoxic-ischemic encephalopathy at post therapeutic hypothermia intervention. This result in the same line with **Tran et al., (2024), & Lemyre and Chan (2018)** who stated that, therapeutic hypothermia has been the standard treatment for moderate/severe hypoxic-ischemic encephalopathy in infants. **Mark & Ru-Jeng (2024)** showed that therapeutic hypothermia is safe and reduced combined outcomes of death and major neurodevelopmental disability by 25% at 18 months of age.

Furthermore, the result of study showed that there was a positive correlation and highly statistical significance between total neonatal body temperature and cerebral oxygen metabolism at pre and post therapeutic hypothermia intervention phases. This finding agreed with **Chowdhury et al., (2025).** " Electroencephalography and optical neuromonitoring predict short-term outcomes in neonates undergoing therapeutic hypothermia

for hypoxic-ischemic encephalopathy"

& Sutin et al., (2023). "Association of cerebral metabolic rate following therapeutic hypothermia with 18-month neurodevelopmental outcomes after neonatal hypoxic ischemic encephalopathy" Who reported that cerebral oxygen metabolism at pre- and post-hypothermia phases increased significantly.

Moreover, there was highly statistically significant relation between neonatal total score severity of hypoxic-ischemic encephalopathy and their gestational age and birth weight at pre and post therapeutic hypothermia intervention phases. This finding was in matching with **Wagdy et al., (2023)** who reported That study population gestational age was; 38±1weeks, birth weight was 3.2 ± 0.4 Kg included: 43% mild, 51% moderate and 6% severe hypoxic-ischemic encephalopathy cases.

Conclusion:

The finding of the present study revealed that there was a positive correlation and highly statistical significance between total neonatal body temperature and feeding tolerance and cerebral oxygen metabolism at pre and post therapeutic hypothermia intervention phases.

Recommendation:

- Training programs for nurses regarding integration of cooling therapy for neonates with hypoxic-ischemic encephalopathy should be conducted in NICUs.
- Continuous research on a larger scale to evaluate the long-term effects of therapeutic hypothermia, both in terms of neurodevelopment and nutritional efficiency in infants.
- The therapeutic hypothermia study should be replicated on a larger random sample in different neonatal intensive care units, for

the generalization of the obtained results.

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