Saúde (SANTA MARIA)

Medicina

DOI: 10.5902/2236583421284

Hypothermia for Neonatal Hypoxic-Ischemic Encephalopathy Using Axillary Temperature: An Effective Treatment in Low Resource Units

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RESUMO

A hipotermia terapêutica é o tratamento padrão-ouro para recém-nascidos com Encefalopatia Hipóxico-Isquêmica (EHI) moderada a grave.

Objetivo: Implementar um protocolo de hipotermia terapêutica utilizando temperatura axilar em recém-nascidos com EHI, comparando a morbimortalidade a curto prazo com um grupo controle histórico.

Métodos: Ensaio-clínico não-randomizado. Foram incluídos no estudo recém-nascidos com asfixia perinatal, a partir de 36 semanas de idade gestacional. O protocolo de hipotermia terapêutica foi aplicado em todos recém-nascidos diagnosticados com EHI, admitidos na Unidade de Terapia Intensiva Neonatal.

Resultados: Seis recém-nascidos foram submetidos à hipotermia terapêutica, sendo seus resultados clínicos comparados com os obtidos em 18 recém-nascidos internados previamente na mesma Unidade (grupo controle). A mortalidade foi menor no grupo de crianças submetido à hipotermia, bem como a presença de desabilidades, na alta hospitalar.

Conclusão: A hipotermia terapêutica para tratamento de recém-nascidos com EHI mostrou ser um procedimento seguro e eficaz, tendo um impacto significativo na redução da mortalidade e de desabilidades na alta hospitalar. O uso da temperatura axilar mostrou-se seguro para monitorizar os recém-nascidos, trazendo benefícios para os pacientes admitidos em Unidades com recursos financeiros limitados.

Palavras-chave: Hipóxia-Isquemia Encefálica; Hipotermia Induzida; Recém-nascido.

ABSTRACT

Therapeutic hypothermia is the standard clinical practice for neonates with moderate to severe hypoxic ischaemic encephalopathy (HIE).

Aim: To implement a therapeutic hypothermia protocol using axillary temperature in newborns with HIE, comparing the short-term outcomes with a historical control group.

Methods: Non-randomized clinical trial. Infants born at 36 weeks gestation with perinatal asphyxia were included in the study. An hypothermia protocol was applied in all neonates diagnosed with HIE admitted to the Neonatal Intensive Care Unit (NICU).

Results: Six newborns underwent therapeutic hypothermia and their clinical outcomes were compared with 18 newborns admitted previously at the same unit (control group). Mortality was lower in hypothermia group as well as the presence of disabilities at hospital discharge.

Conclusion: Therapeutic hypothermia to treat babies with HIE is a safe and effective procedure having a significant impact in reducing the mortality rate and neurological disabilities at hospital discharge. The use of axillary temperature proved to be safe to monitor babies, bringing benefits to the patients in units with low economic resources.

Keywords: Hypoxia-Ischemia, Brain; Hypothermia, Induced; Newborn.

Como citar este artigo:
Binkowski RTK, Silveira ALS, Santos SC, Haeffner LSB, Weinmann ARM. Hypothermia for neonatal hypoxic ischemic encephalopathy using axillary temperature: an effective treatment in a low resource setting. Revista Saúde (Sta. Maria). 2018; 44(1):1-9.

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Data de Submissão: 29/02/2016

Data de aceite: 12/12/2017

Conflito de Interesse: Não há conflito de interesse

INTRODUCTION

Perinatal asphyxia is an injury to the fetus or newborn that occurs more frequently in prepartum/intrapartum period, characterized by oxygen deprivation (hypoxia) and perfusion distress (ischemia) which have negative effects in multiple organs. Among the organs and/or systems affected by asphyxia, the Central Nervous System (CNS) deserves emphasis, with the so-called Hypoxic Ischemic Encephalopathy (HIE). HIE is a major problem worldwide as 10 – 60 % of affected infants die, and at least 25% of survivors have long-term neurodevelopmental sequelae[1].

Clinical trials employing hypothermia in babies with HIE showed that the procedure reduced the occurrence of death and neurological disabilities, without causing major adverse effects. At the same time this procedure increased the number of healthy survivors[2-8].

Despite the clear scientific evidence, there are few Brazilian NICUs employing hypothermia to treat newborns with HIE. The aim of our study was to apply a protocol of therapeutic hypothermia in newborns with HIE and verify the morbidity and mortality during inpatient care, comparing with a historical control group.

METHODOLOGY

Patients and study method: quasi-experimental study (non-randomized clinical trial), with a convenience sample composed of newborns with ≥ 36 weeks of gestational age, admitted within the first 6 hours of age in the NICU of the Santa Maria University Hospital, Brazil, in the period from September 2012 to March 2013. The criteria for initiating the hypothermia protocol was: a) the occurrence of pre/intrapartum asphyxia, confirmed for at least two of the following: a 10-minute Apgar score of 5 or less; assisted ventilation initiated at birth and continued for at least 10 minutes; pH of 7,0 or less in any blood sample or base deficit of 12 mEq/L (mmol/L) in umbilical cord or arterial blood, during the first hour after birth, b) the presence of seizures or moderate/severe encephalopathy, according to modified Sarnat clriteria1,9,10. The exclusion criteria were: birth weight less than 2.000 g, presence of major congenital abnormalities, the possibility of genetic syndromes, active bleeding and/or the lack of parents/legal responsible consent to use the data.

In the above-described period, six newborns were submitted to therapeutic hypothermia (intervention group). This procedure consisted in reducing the newborn's axillary temperature to an average of 33.2°C (varying between 32.7 and 33.7°C), that theoretically correlates to a central temperature of 33.5°C (ideally between 33-34°C). The temperature was measured with an axillar electronic thermometer of decimal precision (manufactured by Incoterm®). In order to achieve this temperature the newborn's heated crib was turned off and, when necessary bags of cooled gel were placed around the head, thorax and shoulders. Hypothermia was maintained for 72 hours and then babies' temperature was gradually increased (at a rate of 0,5°C per hour) by turning on the radiant warmer. During the hypothermia period and afterwards the babies received all the routine care and typical procedures of a NICU.

The control group was formed using the neonatal unit's database, considering the same inclusion and exclusion criteria established for the admission in the hypothermia protocol. We included three times the number of participants in the intervention group, ie, 18 babies with HIE had their records examined.

The study was approved by Santa Maria Federal University Committee on Ethics in Human Research with the number 02598612.1.0000.5346.

Study variables and main outcomes: hypotension, cardiac arrhythmia (bradycardia/tachycardia), persistent acidosis, bleeding, thrombocytopenia, coagulopathy, skin changes and seizures were analyzed in both groups, in two distinct moments: in the first 72 hours (corresponding to the hypothermia period) and after this period until hospital discharge. We also analyzed the use and duration of mechanic ventilation or continuous positive airway pressure (CPAP), the use of inotropes, renal or hepatic dysfunction, hypoglycemia, hydroelectrolytic disorders, early or late sepsis, persistent pulmonary hypertension, thrombosis, fever and the use of antiepileptic drugs during the whole period of hospitalization.

The short term outcomes (that occurred during hospitalization) analyzed included death, time of inpatient care and the occurrence of disabilities. The latter was established according to the use of antiepileptic drugs, necessity of oral-gastric tube for feeding or gastrostomy and an abnormal neurological evaluation at hospital discharge. In the thhypothermia group we also performed the Dubowitz neurological exam11 at the postconceptional age of 41 weeks and analyzed the imaging exams. Statistical analysis: The data were analyzed using the software Stata 10.0. The variables normal distribution was verified with the Shapiro-Wilk test. Comparisons between groups were performed with t-test, Kruskal Wallis test and the

Fisher Exact test. The significant p-value was defined as p< 0,05.

RESULTS:

Twenty-four newborns were analyzed in this study. Six were submitted to the hypothermia protocol (intervention group) and 18 formed the control group. The general characteristics of the babies are summarized in Table 1.

Figure 1 shows the average body temperature during the hypothermia procedure in the intervention group. The temperature was kept stable and within the recommended range of variation during the 72 hours. The minimum value observed was 32°C and the maximum value was 33.8°C.

There was no difference between groups in regard to the use of ventilation support; inotropic drugs; renal, hepatic or metabolic alterations; fever; early or late sepsis; pulmonary hypertension; thrombosis and the need for antiepileptic drugs, during the period of hospitalization.

Table 2 shows the results concerning hypotension, cardiac arrhythmia, acidosis, bleeding, thrombocytopenia, coagulopathy and skin changes, evaluated in two distinct moments.

Hypotension occurred in 100% of the babies submitted to hypothermia and in 22.2% of controls (p=0.001). All babies of the intervention group showed alterations in the coagulation exams and 66.7% of them presented active bleeding. In the control group no alteration was observed in the coagulation exams and only one baby (5.6%) had active bleeding (p<0.001).

After the 72 hours period, thrombocytopenia was the only variable with statistical difference between the two groups: 83.3% of babies in the intervention group presented platelets count below 100.000/mL, against 33.3% of controls (p=0.03).

Table 3 presents the short term outcomes analyzed: death (mortality rate), presence of disabilities and time of inpatient care, independently of HIE degree. The mortality rate was 16.7% in the intervention group and 50% in the control group (without statistical difference). When the mortality rate was analyzed according to the degree of HIE at admission, in babies with severe HIE, death occurred in 25% of the intervention group and in 100% of the controls (p=0.02). In babies with moderate HIE

Table 1 - Maternal and neonatal characteristics

Variables	Hypothermia Group (n = 6)	Control Group (n = 18)	p
Maternal			
Pathologies			
Yes	1 (16.7%)	8 (44.4%)	0.22
No	5 (83.3%)	10 (5.6%)	
Prenatal*			
Yes	6 (100%)	5 (27.8%)	0.009
No	-	5 (27.8%)	
Ignored	-	8 (44.4%)	
Origin*			
Santa Maria University Hospital	2 (33.3%)	11 (61.1%)	0.006
Another hospital of Santa Maria	3 (50%)	0 (0%)	
Outside Santa Maria	1 (16.7%)	7 (38.9%)	
Type of delivery*			
Vaginal	4 (66.7%)	12 (66.7%)	1.0
Cesarean	2 (33.3%)	6 (33.3%)	
Neonatal			
Gender*			

Male	4 (66.7%)	11 (61.1%)	0.8
Female	2 (33.3%)	7 (38.9%)	
Birth weight (g)$	3.185±480	3.128±528	0.4
Gestational age (weeks)$	39.7±1.2	38.5±1.4	0.05
Sarnat*			
Moderate	2 (33.3%)	10 (55.5%)	0.34
Severe	4 (66.7%)	8 (44.4%)	0.72
Age at the beginning of treatment (hours)	5.2±1.0	-	

*Fisher Exact Test.
≠Pathologies: preeclampsia, obesity, premature dislocation of the placenta, asthma and urinary tract infection.
$Student's t-test.

No death occurred to the intervention group, but one baby died in the controls (10%).

No association was verified between elevation of body temperature (fever) and a negative outcome (death and/or disability), although the percentage of death was lower in the group who underwent to hypothermia.

Taking into account the presence of disabilities at hospital discharge, a normal neurological exam was observed in 40% (2) of the intervention group and none of the controls (p=0.04). No difference was observed in relation to the use of antiepileptic drugs or the feeding method, being the majority of babies receiving antiepileptic drugs and oral nutrition.

Table 4 describes the Dubowitz neurological exam11 of the 6 babies submitted to hypothermia. In 2 of these the total score was higher than 30.5 (optimality score).

Fig.1- Mean axillary temperature measurement of the six cooling babies

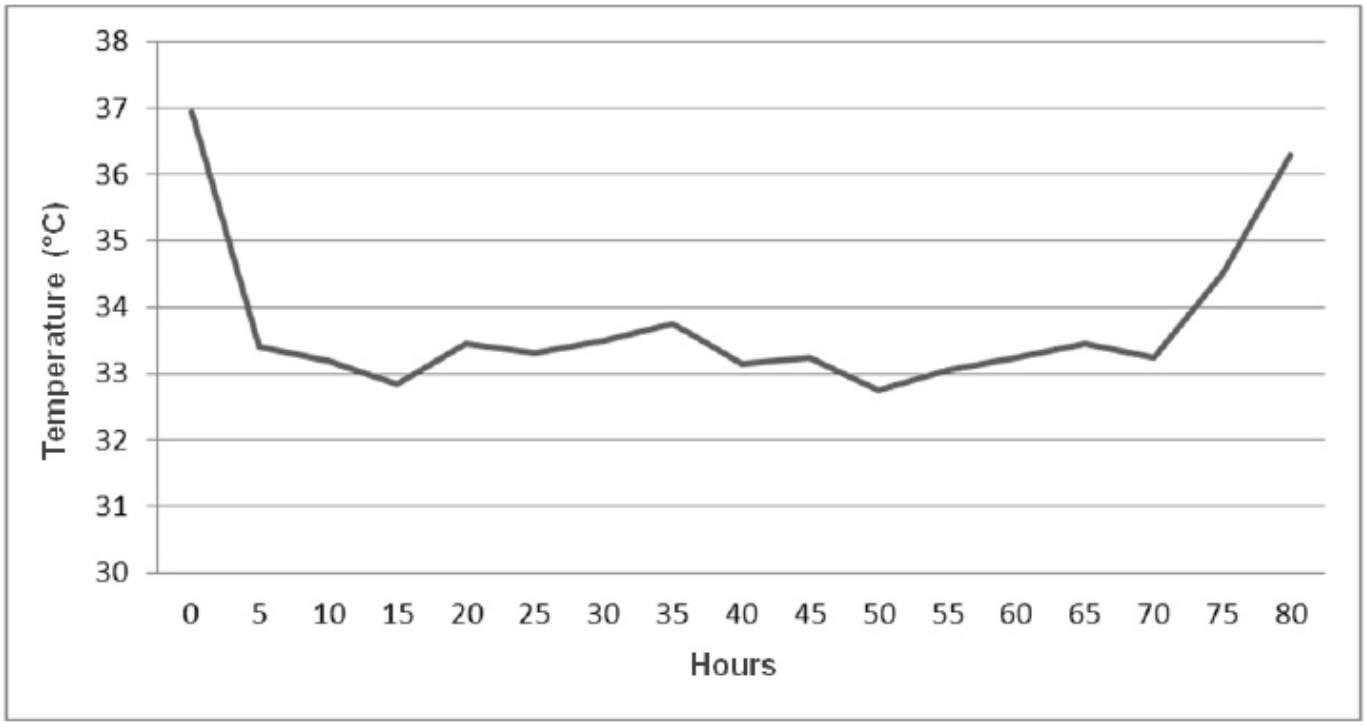

Table 2 - Clinical and laboratory variables analyzed in the first 72 hours (hypothermia procedure) and after the first 72 hours, in both groups.

Variables	Hypothermia group (n = 6)	Control group (n = 18)	p
Hypotension (MAP <40 mmHg)*			
First 72 hours	6 (100%)	4 (22.2%)	0.001
After 72 hours	4 (66.7%)	7 (38.9%)	0.24
Sustained bradycardia (HR < 80 BPM)*			
First 72 hours	2 (33.3%)	1 (5.6%)	0.07
After 72 hours	0 (0%)	3 (16.7%)	0.28
Sustained tachycardia (ventricular extras-systoles)			
First 72 hours	0 (0%)	0 (0%)	
After 72 hours	0 (0%)	0 (0%)	
Persistent acidosis (pH < 7,15 for longer than 3 hours)*			
First 72 hours	2 (33.3%)	3 (16.7%)	0.38
After 72 hours	0 (0%)	3 (16.7%)	0.28
Bleeding*			
First 72 hours	4 (66.7%)	1 (5.6%)	0.001
After 72 hours	2 (33.3%)	3 (16.7%)	0.38
Trompocytopenia (platelets < 100.000/mL)* ≠			
First 72 hours	3 (50%)	5 (27.8%)	0.31
After 72 hours	5 (83.3%)	6 (33.3%)	0.03
Coagulopathy (PT >1,5 or PTT> 60s.)*			
First 72 hours	6 (100%)	0 (0%)	0.000
After 72 hours	1 (16.7%)	0 (0%)	0.07
Skin changes$			
First 72 hours	0 (0%)	0 (0%)	
After 72 hours	0 (0%)	0 (0%)	

*Fisher Exact Test.

≠A cut-off point of less than 100.000 platelets/mm3 for thrombocytopenia was adopted based on standard laboratory procedures of our service.

$Skin changes: presence of erythema, cyanosis or subcutaneous fat necrosis.

Table 3 - Short-term outcomes (during hospitalization and at discharge), in both groups

Variables	Hypothermia group (n = 6)	Control group(n = 18)	p
Seizures*			
First 72 hours	5 (83.33%)	16 (88.9%)	1
After the first 72 hours	2 (33.3%)	8 (53.3%)	0.63
Use of antiepileptic drugs at discharge*	4 (80%)	7 (77.8%)	1
Number of antiepileptic drugs at discharge	1	1	-
Time of inpatient care (days) ≠	37.8±18.4	31.4±11.3	0.21
Feeding method at discharge*			
Oral	3 (60%)	7 (77.8%)	0.68
Nasal/oral gastric tube	1 (20%)	2 (22.2%)	
Gastrostomy	1 (20%)	0 (0%)	
Neurological exam at discharge *			
Normal	2 (40%)	0 (0%)	0.04
HIE in any degree	3 (60%)	9 (100%)	
Death*	1 (16.7%)	9 (50%)	0.34
Death in patients with temperature >37,2°C e <37,8ºC*	1 (16.7%)	7 (43.7%)	0.35
Death in patients with temperature ≥37,8ºC*	1 (20%)	8 (50%)	0.34
Patients with severe HIE*			
N	4 (66.7%)	8 (44.4%)	0.72
Death	1 (25%)	8 (100%)	0.02

*Fisher Exact test.
≠ Student'st-test.

Table 4 - Results of Dubowitz neurological exam performed at 41 weeks of postconceptional age in cooled babies Patients

		Patients					
Categories	Optimality score	1	2	3	4	5	6
Tone	≥9	10	6	2	10	0	3
Tone Patterns	5	4	4	4	4	0	2
Reflexes	≥5	5	5	1	5.5	0	0
Movements	3	3	2.5	2	3	0	0
Abnormal signs	3	3	3	1	3	0	0
Behavioral Items	≥6	7	6.5	3.5	7	0	0
Total	≥30.5	32	27	13.5	32.5	0	5

DISCUSSION

Because it is a relatively new treatment, there is still a limited number of NICU using hypothermia as a routine procedure to treat babies with HIE in Brazil. One reason for this may be the cost for the acquisition of the equipment, since in our country economic resources are limited in many units. In our study we utilized a simple method of hypothermia, previously described and successfully implemented by Jacobs et al.5. However we used axillary temperature measurement instead of central temperature in order to monitor the procedure.

The use of axillary temperature to monitor babies undergoing hypothermia seems to be a viable option especially in places or units where economic resources are limited and have also a higher rate of mortality due perinatal asphyxia. In a systematic review, Craig et al.12 found an average difference of only 0.17ºC between the axillary

and rectal temperatures of normothermic newborns. Recently, Horn et al.[13] compared skin temperature to rectal temperature in newborns submitted to hypothermia and observed a good correlation between them again. The same was observed by Thomas et al.14, in a study published in 2012, although the authors observed that around 40% of the values were outside the target interval, between 33-34°C. Therefore the babies with temperatures less than 33ºC would be susceptible to an increase in the adverse effects of hypothermia, and those having temperatures above 34ºC could lose the neural-protection due to the procedure. For this reason, the authors did not recommend the use of skin temperature measurement instead of rectal temperature during the hypothermia period. It must be emphasized that in Thomas et al.' study the axillary temperature was measured by different nurses, which could represent a bias in the results (interobserver variability).

In a very similar study15 like ours the authors also demonstrated the possibility of safely cooling babies using a low cost procedure, suggesting as a good option for places with limited economic resources. However, these authors considered as ''few resources'' the condition of having a single rectal probe available in the unit, which does not correspond to the reality in many Brazilians neonatal units. In our study we did not find side effects of hypothermia nor neural protection loss even having measured the axillary temperature.

Hypotension and thrombocytopenia were observed during the hypothermia period, a result that is consistent with a systematic review with a small patient sample2. It must be emphasized however that these and other conditions (ie, bleeding and coagulopathy) did not result in more serious adverse events in our babies.

All these factors suggest that the results of clinical trials in which there is no difference in the occurrence of major clinical complications among groups3,5,16,17 are due to an adequate monitoring of the controls. This should be taken into account when using a historical control group.

It is important to note that the clinical and neurological outcomes observed in our babies correspond to a short-term assessment, i.e. during the hospitalization period or at discharge. We believe that this can be the reason for the lack of significant statistical differences for some of the relevant outcomes analyzed, since the period of stimulation and

rehabilitation could not yet be assessed.

Despite these limitations, we consider that two results must be highlighted. When the analysis was refined, taking into account the severity of HIE, we observed a statistically significant reduction in mortality rate among cooled babies with severe encephalopathy (75% of survival against 0% in the control group). The second result that must be highlighted concerns the Dubowitz neurological exam (performed at 41 weeks of postconceptional age) and the routine neurological exam at the moment of hospital discharge, in cooled babies. The two babies with moderate HIE at admission both presented a normal neurological exam and no alterations in the image exams.

CONCLUSION

Although core temperature is considered the gold standard for monitoring babies treated with hypothermia, our results suggest the use of axillary temperature is safe, viable and brings benefits to the patients in places where the rectal probe is not available.

Abbreviations used

HIE: hypoxic ischaemic encephalopathy
NICU: neonatal intensive care unit
CNS: central nervous system
CPAP: continuous positive airway pressure
MAP: mean arterial pressure
HR: heart rate
BPM: beats per minute
PT: prothrombin time
PTT: partial thromboplastin time

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