ECRONICON OPEN ACCESS

EC PAEDIATRICS
Research Article

53 Newborns with Hypoxic Ischemic Encephalopathy Treated with Hypothermia Therapy Using Neonatal Laminar Flow Unit

Perez JMR*

International Neurodevelopment Neonatal Center (CINN), Sao Paulo, Brazil

***Corresponding Author:** Perez JMR, International Neurodevelopment Neonatal Center (CINN), Sao Paulo, Brazil.

Received: September 26, 2018

Abstract

Aim: The aim of this trial was to do clinical observations of newborns diagnosed with Hypoxic Ischemic Encephalopathy and treated with hypothermia therapy with the Neonatal Laminar Flow Unit [1].

Methods: The trial included 53 newborns, delivered in the same hospital as they received the treatment, under 35 weeks of gestation and with up to 6 hours of life. Total body cooling was achieved using the neonatal laminar flow unit for 72 hours, with continuous rectal temperature servo control, isolation and humidification. Outcome measures were cerebral palsy, a Bayley II Mental Development Index score < 70, hearing loss or blindness. We compared findings with previously published studies [2-4].

Results: We included 53 newborn infants (73% male) with a birthweight of 2389 ± 557gr and gestational age of 38 ± 3.4 weeks. To classify the severity of Hypoxic-Ischemic Encephalopathy, we used the Siben Neurologic Score [5] and the Sarnat grading scale [6]. The majority of newborns (71%) were diagnosed with severe HIE, after assessment of the Siben Neurologic Score, and the remaining newborns (29%) were diagnosed with moderate HIE, following the same assessment. Each of those diagnostics were confirmed after assessment of the Sarnat score.

Total body cooling (33 - 34°C) was achieved in 75 minutes and maintained with servo control.

The mortality was 28.3% (15 newborns), at 18 - 24 months of age, five of the 38 survivors were diagnosed with cerebral palsy(9.4%), two were diagnosed with blindness (3.7%) and five with impaired hearing (9.4%).

Conclusion: Because these results were in the same range as those reported by other studies [2-4], we conclude that the use of the Neonatal laminar flow unit to supply total body hypothermia therapy in newborns with HIE was effective.

Keywords: *Hypoxic Ischemic Encephalopathy; Hypothermia Therapy; Neonatal Laminar Flow Unit*

Introduction

The incidence of the Hypoxic Ischemic encephalopathy as a result of perinatal asphyxia is very variable around the world, currently, perinatal asphyxia associated with moderate or severe HIE, which is its main complication, affects between 1 - 2/1,000 live births in developed countries and is estimated at affecting between 10 - 20/1,000 live births in poor or developing countries [2] being responsible for 1/3 of neonatal mortality in these countries.

Previous trials have described treatment of HIE with hypothermia with the use of cool caps and total body cooling with blankets and ice [3,4]. Therapeutic hypothermia improves outcomes for many babies promoting significant reductions in death and disability at 18 months, as proven by these previous clinical trials.

The use of hypothermia therapy has been proven effective and its use is increasing, but unfortunately it's use is very uneven between developed and poor or developing countries. In poor or developing countries is common not managed hypothermia therapy or the use of the passive hypothermia or active hypothermia with artisanal methods (ice, cold water bottles, fan etc.) with all the risks inherent to its use or than non-effectiveness [5]; already in developed countries the use of the passive hypothermia is common only during transport of the newborn, but in NICU is customary to use servo controlled mattress, being that cool cap has been left aside because of their difficult handling.

The use of the laminar flow unit was described in two articles [6,7], including its use to supply hypothermia therapy. There were two primary outcome variables in this descriptive proof-of-concept trial that focused on infants who were born with moderate or severe HIE.

The first was to assess the efficacy of the unit in achieving and maintaining low body temperature in actual clinical practice and the second was to assess the combined endpoints of death or moderate or severe disability. The paper reports the results on the use of this novel laminar flow device to deliver total body moderate hypothermia to infants with hypoxic ischemic brain injury and to compare the results to the published literature.

Methods

This is a descriptive cohort, clinical proof-of-concept study conducted in three neonatal centers that achieved total body cooling with the use of the neonatal laminar flow unit, medical device that has been described in two previous publications [6,7]. All infants considered potential candidates to undergo hypothermia treatment were subject to a detailed standardized two neurologic examination; Siben's Score [1] and Sarnat's Score [8] and all infants with at least one of the two scores (Siben or Sarnat) for moderate or severe Hypoxic Ischemic Encephalopathy and metabolic acidosis with a pH < 7.1, requiring ventilatory support. Upon informed consent, infants with 35 weeks or more of gestational age presenting with HIE within six hours of birth were included; no electroencephalogram (EEG or a.EEG) was obtained before inclusion or during the treatment.

We then provided total body cooling by convection heat, while measuring the neonate's rectal temperature by servo control. The target temperature was 33ºC - 34ºC within 60 - 70 minutes and added isolation and humidification was supply as previously published description of the medical device [6,7]. Continuous rectal temperature was performed for the entire duration of the 72-hour study in order to ensure precise servo control. Intermittent monitoring of skin temperature was monitored was performed, was although it was not used to make any adjustments to the hypothermia treatment. Rewarming started slowly after 72 hours of hypothermia, by means of a stepwise adjustment of the servo control set point at 0.5°C per hour. During the 72-hour intervention period, and until discharge, infants were also monitored for cardiac arrhythmia, hypotension, persistent or worsening acidosis, major-vessel thrombosis or bleeding, skin changes and death.

We verified the equipment's performance on an hourly basis Magnetic resonance imaging (MRI), was performed before discharge, between eighth and twelfth days of live. A pediatric radiologist assessed the imaging results while unaware of the clinical treatment. We scheduled detailed neurologic and developmental evaluations for 12 and 24 months of age, based on well-described criteria, which was carried out for all high-risk infants. Accepted criteria were used to define cerebral palsy [9] while assessing the Bayley II Mental Developmental Index (MDI) [10]. A major disability was defined as cerebral palsy and, or, the following: an MDI score ≤ 70, blindness, hearing impairment requiring a hearing aid and a persistent seizure disorder.

The staff in charge of obtaining written informed consent from parents was not involved in the study, which was approved by the ethics committee of the three aforementioned centers, the Stella Maris Hospital, São Miguel Maternity and Casa de Saúde Guarulhos in São Paulo, Brazil.

In view of available previous data on hypothermia, albeit using a different technology, denying potentially effective treatment to some of the infants in the absence of other alternatives was considered unacceptable by the ethics review board.

We compared our results with a study published previously [7] and with two meta-analyzes published [11,12].

Results

We included 53 newborn infants (73% male), with a diagnosis of either moderate or severe HIE, for which the diagnosis was arrived at with both neurological scores for reborn infants (Siben and Sarnat). We found overlapping diagnostics for both scores in over 90.5% of cases (48 newborns). Of the remaining 5 infants, 3 presented a mild Sarnat score, and a moderate Siben score; and 2 presented a mild Siben score, and a moderate Sarnat score. All 5 infants received treatment, as they had at least one moderate score. We started treatment with laminar flow hypothermia when they were 4.15 ± 1.20 hours or age, measurement of neonates´ mean rectal temperature was 36.8 ± 0.7°C at baseline, which was smoothly lowered to between 33°C-34°C in 70 ± 15 minutes without overshooting. Rectal temperatures remained steady on subsequent measurements throughout the duration of the 72-hour treatment. Low variability was observed in sequential temperature measurements throughout this period. Sequential temperature measurements throughout this period showed low variability: mean coefficient of variation was 0.014 (95% CI: 0.012 - 0.017) and the mean overshoot did not exceed 0.34^0C. Target rectal temperature was maintained by ± 0.5^0C for 96.6% of the time. This compares very favorably with the results from other cooling methods that used temperature servo control. After 72 hours we started rewarming, which was carried out as described in the Methods section without overshoots during cooling or rewarming. A summary of clinical data is found in table 1.

Weight (grams) 2389 ± 557
Apgar score [median (range)]
1 minute 1 (0 - 4)
5 minutes 4 (0 - 7)
10 minutes 6 (3-9)
Siben score: Severe HIE prevalence (71% - 38 newborns); moderate HIE (29% - 15 newborns)
Sarnat score: Median (range) 3 (2 - 3)
Associated conditions, n (%)
Pulmonary hypertension 8 (15.09%)
Early sepsis 24 (45.2%)
Seizures 30 (56.6%)
Hypotension or shock requiring vasopressors 37 (70%)
First pH, mean (range) 6.9 (6.5 - 7.19)
Mean (IQR) 7.02 (6.9 - 7.18)
First base deficit (mmol/L) -17 ± 5.1

***Table 1**: Clinical data on 53 neonates with HIE.*

All infants weighted above 1.800 grams, presenting a low Apgar score at one and five minutes of age. Moderate encephalopathy was present in 29% of the treated infants and severe HIE was present in 71%. The occurrence of seizures was of 56.6%, We observed the following associated conditions during initial presentation: early sepsis (45.2%), persistent pulmonary hypertension (15.09%), hypotension or shock which required vasopressors (70%). Heart rate decreased during cooling to a mean of 90 beats per minutes, reaching < 70 in 55% (29 infants), in these cases we need to introduce vasoactive drugs. There is no record of other dysrhythmias, cutaneous signs of cold injury were not noted in any infant and there was no clinical or biochemical evidence of renal or hepatic injuries, other than those that were initially seen at the presentation of HIE. Initial oliguria and elevation of hepatic enzymes were all transient. Our outcome data are summarized in table 2. The mortality rate was 28.3% (15 newborns), with five infants died during the hypothermia treatment and the other six after completion of the treatment. There was no infant withdrawal from the treatment due to asphyxia brain injury. We examined all the 38 survivors at 18 months and 29 of them at 24 months, four newborns (13.7%) were diagnosed with cerebral palsy - three severe and 1 mild - three newborn (10.34%) had hearing impairment and two infants had visual impairment (6.8%), and finally one infant presented persistent seizure disorder (3.4%). MRI abnormalities were found in four infants (13.7%).

	Tagin., et al.	Jacobs., et al.	1Perez., et al.	2 Perez
Severity HIE				
Moderate	54%	63%	38%	29%
Severe	46%	37%	62%	71%
Other Results				
Death	26%	25%	31%	28.3%
Death or major disability	48%	46%	42%	42%
Cerebral palsy	19%	17%	8%	13.7%
Hearing impairment	4%	3%	4%	10.34%
Blindness	6%	3%	0%	6.8%

Table 2: *Comparison between Tagin., et al. [11], Jacobs., et al. [12], 1Perez., et al. [7] and 2 Perez (this trial).*

Rates of moderate or severe HIE in our series of infants and outcomes were also compared to those reported in two meta-analyses of hypothermia [11,12] in neonates presenting with HIE (Table 2). Occurrence of the combined outcome of death or moderate or severe disability was 42%, these outcomes were comparable to those reported in the two meta-analyses and the our publication previously published.

Discussion

We described how 53 infants with HIE were treated using a neonatal laminar flow unit that provides servo-controlled hypothermia by laminar flow. The laminar flow unit was proven effective in achieving and maintaining moderate total body hypothermia under well controlled conditions and with little body temperature fluctuation in newborns with HIE. It should also be noted that the mortality and neurologic disability rates in this descriptive study show outcomes similar to those found in the previous literature by means of other cooling methods.

We have used two neurological scores to deepen our clinical assessment of newborns (Siben neurological score and Sarnat score), considering the impossibility of having access to the use of the EEG or a.EEG to assist in the evaluation of HIE; unfortunately the use of the a.EEG is too expensive for poor or developing countries; On the other hand, we believe that the best way to diagnose HIE is by clinical examination, and therefore by deploying two neurological scores we will achieve a more accurate clinical diagnostic. It is important to notice, nonetheless, the challenge in diagnosing convulsive crises without the EEG.

The eligibility criteria for this trial were designed to include infants with acute HIE presenting with a high probability of a poor outcome, including death or disability, and with routine intensive care. The 38 infants were severely ill on admission and at the time they were enrolled to the study (Tables 1 and 2). The severity of their conditions was similar to that described in other studies, with moderate or severe encephalopathy and intrapartum hypoxia-ischemia and low Apgar scores, on-going resuscitation, cord or arterial blood gas within one hour of birth with a pH of < 7.1 and, or, a base deficit higher than 12 [2,13,14]. It is possible to cool the brain by cooling the body, selectively cooling the head or cooling both head and body. Homogenous cooling to all brain structures is achieved by whole-body cooling, such as peripheral and central brain regions. We can achieve greater cooling of the periphery of the brain than the central brain structures by means of selective head cooling. Whole-body cooling appears to be more common for daily use for a number of reasons, such as consistent reduction in brain temperature in said structures. Reports show that selective head cooling is more related to a higher frequency and a higher severity of hypoxic-ischemic lesions than with whole body cooling following therapeutic cooling. It is believed that this is an additional potential advantage to the laminar flow unit, even in the absence of deep temperature probe studies in animals.

Laminar flow achieves total body cooling by means of convection with a simple servo control, so accepted article that the hypothermia maintained with minimal nursing intervention.

This cooling system has been proven to be easily initiated, adequately achieve target temperature in a controlled and timely manner with no overshoots and require minimal effort by care providers. Cooling was very well tolerated and no serious adverse events are associated. Noise levels are below 60 decibels, humidity is maintained at around 60-70%, and air velocity is about 0.45 meters per second with continuous isolation**.** A number of the disadvantages is associated with other methods that have achieved whole body hypothermia: no servo control, high fluctuations in target temperature and, or, the need for frequent temperature adjustments Laminar flow achieves total body cooling using convection with a simple servo control, so that the maintenance of hypothermia can be achieved with minimal nursing intervention.

Our findings show that this cooling system was easily initiated, adequately achieved the target temperature in a controlled way and in a timely manner without overshooting and required minimal effort by care providers. Cooling was very well tolerated and not associated with serious adverse events. The noise of the unit is lower than 60 decibels, the humidity is maintained at around 60 - 70%, the air velocity is about 0.45 meters per second, and the isolation is continuous.

Other advantages of the laminar flow unit are that the equipment uses convection heat, rather than conduction or radiant. For over 100 years we have known that the best way to provide heat to the newborn is through convection heat; therapeutic hypothermia achieved through convection heat has few cases of excessive cooling. In this study, we did not witness a single case of subcutaneous necrosis, which may occur with some frequency when therapeutic hypothermia is achieved through conduction. We also did not witness an increase in insensitive losses, of typical occurrence when using a radian- heat cradle when providing heat to the newborn [15-17].

We would like to emphasize that the unit was found to be convenient to use and not unduly time-consuming by our nurses, an important characteristic in low-resource settings. Another important aspect is that the unit can double as a neonatal bed for sick neonates that do not required hypothermia, as it offers significant humidity, unlike a radiant warmer. This may be an important advantage in low- resource settings. Supportive intensive care is the only treatment available in many regions of the developing world and high costs prevent the use of cooling equipment. That accounts for the death of many infants with severe encephalopathy and many, if not all, of the survivors are handicapped. In Brazil, for example, the incidence of HIE varies widely, between five and 25 per 1000 live births, and the real rate of sequelae is unknown. This study was restricted by more than one factor; firstly, it was a descriptive study; secondly, as we all know, the absence of an EEG limits the clinical team access to a better diagnostic of the newborn's convulsive crises. Thirdly, we did not have access to a larger sample and our quantitative estimates of the incidence of the various outcomes did not achieve a high degree of precision.

The study also raised ethical issues that we would recommend others to take into consideration when designing further studies

Conclusion

This is a second trial about the use of the neonatal laminar flow unit to supply hypothermia therapy in newborns with HIE. In this trial ours initial observation are maintained, with little body temperature fluctuations and under well controlled conditions. Mortality and neurologic disability rates similar to outcomes reported in the literature for other cooling methods have been demonstrated by this descriptive study. It is a very simple-to use equipment and which should be considered for treating many infants in different regions of the world due to its low cost.

Conflict of Interest

I am one of the patent holders of the Neonatal Laminar Flow unit.

Acknowledgment

I would like to thank Mr. Denis Cavalcanti Coutinho Mani for the revision the text in English.

Bibliography

1. Perez JMR., *et al*. "Clinical hypoxic-ischemic encephalopathy score of the Ibero American Neonatology Society (Siben): A new proposal for diagnosis and management". *Revista da Associação Médica Brasileira* 63.1 (2017): 64-69.

2. Lawn J., *et al*. "No cry at birth: global estimates of intrapartum stillbirths and intrapartum-related neonatal deaths". *Bulletin of the World Health Organization* 83.6 (2005): 409-417.

3. Gluckman PD., *et al*. "Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicenter randomised trial". *Lancet* 365.9460 (2005): 663-670.

4. Azzopardi D., *et al*. "Whole body hypothermia for the treatment of perinatal asphyxial encephalopathy: a randomised controlled trial". *BMC Pediatrics* 8 (2008): 17.

5. Pauliah SS., *et al*. "Therapeutic hypothermia for neonatal encephalopathy in low and middle-income countries: a systematic review and metaanalysis". *PloS ONE* 8.3 (2013): e58834.

6. Perez JMR., *et al*. "A laminar flow unit for the care of critically ill newborn infants". *Medical Devices* 6 (2013): 163-167.

7. Perez JMR., *et al*. "Using a novel laminar flow unit provided effective total body hypothermia for neonatal hypoxic encephalopathy". *Acta Pediatrics* 104.11 (2015): e483-e488.

8. Sarnat HB and Sarnat MS. "Neonatal encephalopathy following fetal distress". *Obstetrical and Gynecological Survey* 32.5 (1977): 295.

9. Surveillance of Cerebral Palsy in Europe (SCPE). "Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers". *Developmental Medicine and Child Neurology* 42.12 (2000): 816-824.

10. Bayley N. "Bayley Scales of Infant Development, 2nd edition". San Antonio, TX: Psychological Corp (1993).

11. Tagin MA., *et al*. "Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta-analysis". *Archives of Pediatrics and Adolescent Medicine* 166.6 (2012): 558-566.

12. Jacobs SE., *et al*. "Cooling for newborns with hypoxic ischaemic encephalopathy". *Cochrane Database of Systematic Reviews* 1 (2013): CD003311.

13. Hoque N., *et al*. "A comparison of cooling methods used in therapeutic hypothermia for perinatal asphyxia". *Pediatrics* 126 (2010): e124-e130.

14. Shankaran S., *et al*. "Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy". *New England Journal of Medicine* 353.15 (2005): 1574-1584.

15. Sarkar S., *et al*. "Distribution and severity of hypoxic-ischaemic lesions on brain MRI following therapeutic cooling: selective head versus whole body cooling". *Archives of Disease in Childhood - Fetal and Neonatal Edition* 97.5 (2012): F335-F339.

16. Robertson NJ., *et al*. "Techniques for therapeutic hypothermia during transport and in hospital for perinatal asphyxial encephalopathy". *Seminars in Fetal and Neonatal Medicine* 15.5 (2010): 276-286.

17. Thorensen M. "Supportive care during neuroprotective hypothermia in the term newborn: adverse effects and their prevention". *Clinics in Perinatology* 35.4 (2008): 749-763.

Volume 7 Issue 11 November 2018
©All rights reserved by Perez JMR.