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Original article

Therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy: temperature control during transport

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Abstract

This study aims to assess the adequacy of temperature control during transport of patients referred for therapeutic hypothermia at our centre and to evaluate the occurrence of complications when temperature control is not adequate. Transport data of patients (n = 37) referred during a period of 30 months was reviewed retrospectively, as well as our prospectively collected database of infants treated with hypothermia. We evaluated duration of transport, incidence of excessive cooling on admission and associated complications. Distance from the referring hospital and duration of the transport were not associated with excessive cooling. We then divided patients into two groups according to adequacy of temperature control during transport depending on the presence or absence of regular temperature recordings and compared study variables between the groups. A significant correlation was found between the lack of adequate temperature records during transport (n = 19) and excessive hypothermia on admission (42% vs. 11% for the group with adequate temperature monitoring). There was a trend towards increased incidence of coagulation problems for infants who had admission temperatures below 32.0°C.

Passive cooling is simple and effective to ensure early achievement of neuroprotective temperature, but continuous temperature monitoring during transportation is mandatory in order to avoid excessive cooling.

Keywords

Hypothermia, hypoxic-ischemic encephalopathy, neuroprotection, newborn, temperature, transport.

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What is known?

- Therapeutic hypothermia is a safe and effective therapy for moderate to severe hypoxic-ischemic encephalopathy.
- Neuroprotective temperatures should be attained as soon as possible.
- Effectiveness and safety of this therapy can be enhanced by the use of evidence-based guidelines.

What is new?

- Strict protocols for passive hypothermia in referring hospitals and during transport will enable timely achievement of neuroprotective temperatures and can avoid excessive hypothermia that can be associated with complications.
- The protocol should be carefully followed under guidance of the intensive care unit team and the transport team, even for short distances.

Introduction

Despite adequate pre- and perinatal care, incidence of hypoxic-ischemic encephalopathy (HIE) in developed countries is still significant, remaining relatively unchanged at a rate of around 1.5 per 1,000 live births [1].

The risk of death and moderate to severe disability was very high before the generalized use of therapeutic hypothermia (TH) [2]. TH was shown to reduce significantly mortality and neurodevelopmental problems [3, 4].

Current guidelines recommend that, in order to obtain maximal benefits, hypothermia should be started as soon as possible and within 6 hours after the insult [5]. Therefore, it is often necessary to transport the newborn from remote sites to a center providing TH, and this raises the issue of initiating hypothermia at the referring hospital or during transport [6]. Early establishment of TH is associated with improved outcomes [7].

Servo-controlled active cooling has been shown to improve temperature stability [8], allowing rapid attainment of target temperatures compared with previously reported methods [9], and to minimize risk of overcooling [10]. The use of a servo-controlled system allows the team the freedom to focus on the critical care [10], and this can be particularly important during the transport of infants for TH [11].

Nevertheless, few neonatal transport systems have adopted servo-controlled hypothermia during transport, and most babies referred for TH are transported in passive hypothermia. Reasons for this option are mainly its costs and the fact that a neuroprotective temperature can be achieved by passive cooling [12], despite the risk of wider variations in temperature [13]. To minimize that risk, continuous monitoring of a central temperature is mandatory [11].

Guidelines for cooling during neonatal transport were recently published, on the basis of current literature and evidence from the TOBY and ICE trials [14].

Despite the clear benefits of hypothermia, there is a need to further research on particular aspects, including the definition of the age limit to start TH [2], though it is well accepted that earlier is better. The importance of using servo-controlled systems during transport [15], the best temperature for neuroprotection, the best method of cooling and the best duration of TH are other aspects that might be further investigated in research trials [2].

In this study, we aim to investigate the association between the adequacy of temperature monitoring during transport and the risk of excessive cooling on admission, as well as the occurrence of significant side effects of excessive cooling in patients treated at our NICU with TH.

Methods

We retrospectively analyzed transport data for all infants treated with TH at our NICU during a 30-month period (January 2010-June 2012), focusing on the time between birth and the start of active hypothermia. Our NICU introduced TH in our country and initially it worked as a nationwide TH program for 6 months, followed by a second NICU in the same city, so during most of the study period the referrals could come from any place in the country. At our NICU we adopted

a protocol that is very similar to the TOBY trial protocol, including the use of amplitude-integrated electroencephalography (aEEG) changes (baseline or seizures) for the final decision to treat [15].

In addition to the basic parameters of neonatal care, our database includes information on the clinical and laboratory monitoring and complications during treatment. We also collected data on temperature monitoring during transport, distance and duration of transport between hospitals and rectal temperatures at the time of referral to TH, at the beginning of the transport, during transport and on arrival at the hypothermia center.

To study the influence of the distance travelled and duration of transport on the temperature variations, we considered a cut-off point of 100 kilometers from the treatment center.

In order to evaluate the influence of temperature monitoring during transport, we grouped infants according to the adequacy of transport temperature data records. We considered adequate temperature monitoring when rectal temperature readings were documented during transport every 15 minutes until arrival at our NICU (group A), and inadequate monitoring when such information was not clearly documented on the transport records (group B).

For the purpose of this study, rectal temperatures ≥ 37.0ºC are considered as hyperthermia, 35.1º-36.9ºC as normothermia, 33.0º-35.0ºC as neuroprotective temperature and < 33.0ºC as excessive hypothermia.

Finally, we studied in infants the incidence of complications according to the lowest temperature recorded between birth and start of actively induced hypothermia.

Statistical analysis was performed with IBM SPSS® 20.0. Significant differences were considered when p-value was below 0.05.

Results

During the study period, 40 infants were treated in our NICU with TH. The median (range) of the birthweight and gestation was 3,025 grams (1,738 to 4,600) and 39 weeks (36 to 41). Median (range) pH during the first hour of life was 6.94 (6.5 to 7.33) and median (range) Apgar scores at 5 and 10 minutes were 4 (0 to 10) and 5 (0 to 10), respectively. The incidence of severe and moderate HIE was 40 and 42%, respectively, and the incidence of mortality was 13%.

Three infants were inborn, thus 37 infants required postnatal transfer and were analyzed in our study. Eighty-one percent started passive cooling during the first hour of life and 19% started passive cooling between 1 and 6 hours. Our NICU was contacted for referral during the first hour after birth in 54% of cases.

Despite median transport time being 90 minutes (range 9-213), 38% of the outborn patients arrived at our NICU more than 6 hours after birth. Aspects related to relevant timings of transport are depicted in **Fig. 1**.

Treated infants were transferred from a median distance of 134 km (range 3-420) and the median of transport time was 1.5 h (range 0.2-3.9 h). Fifty-one per cent were born more than 100 km away from the treatment center (maximal transport distance 420 km), arriving at our NICU with a median temperature of 33.9ºC (range 27.5-36.2ºC), whereas infants born at less than 100 km arrived at our NICU with a median temperature of 33.4ºC (range 29.4-35.6ºC). Excessive hypothermia was detected in 26% of infants transported for more than 100 km, and in 28% of infants born at less than 100 km, showing the absence of association between transport distance and the occurrence of excessive cooling. **Fig. 2** shows the distance and duration of transport in two different groups: newborns with temperature on arrival < 33.0º and 33.0-37.0º.

After separating infants into two groups according to adequacy of transport data recordings,

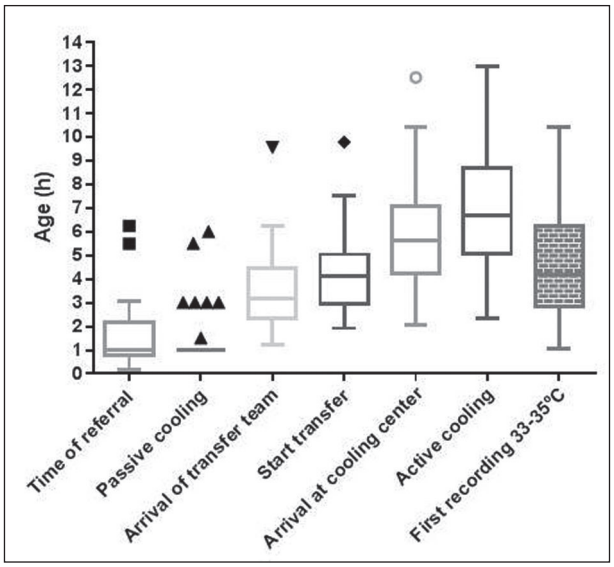

Figure 1. Relevant timings during transport for TH: timing of referral, arrival of the transfer team, arrival at the cooling center, onset of passive cooling and active cooling and age at which the rectal temperature documented was in the range 33.0ºC to 35.0ºC. Note: 12 infants had no record of the arrival time of transfer team.

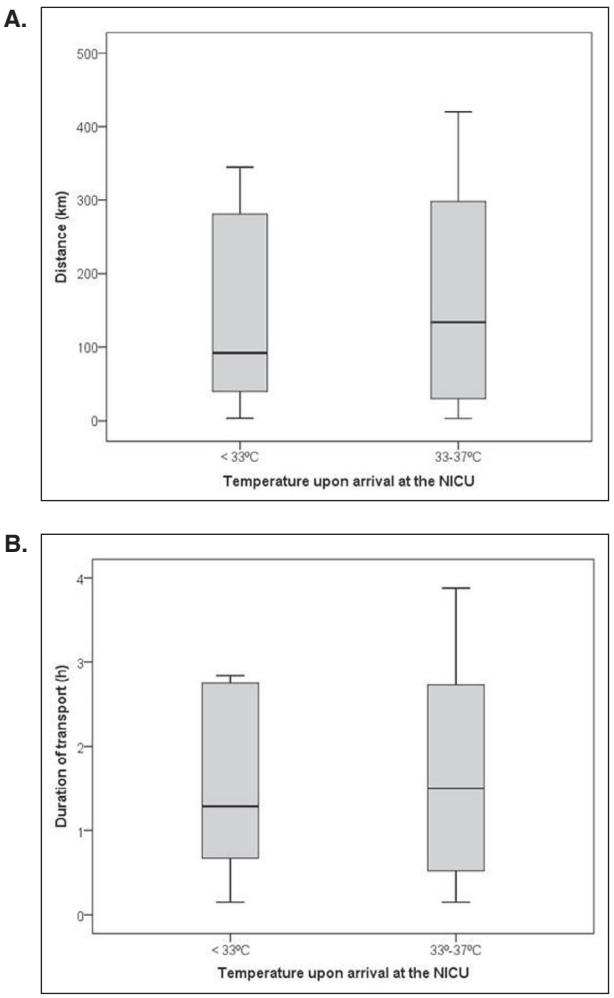

Figure 2. Relationship between distance (**A**) and duration (**B**) of transport vs. temperature upon arrival at the NICU in two different groups: newborns with temperature on arrival < 33.0ºC and 33.0-37.0ºC.

we identified adequate transport records in 18/37 patients (group A) and inadequate transport data in 19/37 (group B). Available individual temperature records are depicted in **Fig. 3** and comparison between the two groups in **Tab. 1**.

Excessive hypothermia on arrival at the hypothermia center was more frequent in group B (42% vs. 11%, $p < 0.03$). Neuroprotective temperatures on arrival were more frequent in group A (83% vs. 37%, $p < 0.02$).

Considering all measurements from group A, 39% experienced excessive hypothermia at least once, but only 6% had a temperature ≤ 32.0ºC.

In group B, the lowest recorded temperature was 27.5°C. Considering all existing measurements in this group, 63% experienced excessive hypothermia at least once and 53% experienced temperatures ≤ 32.0°C. Temperatures ≤ 32.0°C were more frequent in group B (6% vs. 53%, $p < 0.02$).

In our sample, the infant with the lowest temperature (27.5ºC on arrival to the treatment center) arrived at 8.7 hours of life and only managed to reach a temperature above 33.0ºC at 18 hours of life.

Despite relatively late beginning of TH at median age of 7 hours of life (range 2-13 h), 83% of infants with adequate transport records had a reading of neuroprotective temperature before 6 hours (**Fig. 1**).

When looking at eventual adverse effects of excessive cooling, we found no statistically significant difference between groups in the incidence of seizures, hypotension and coagulopathy that could be related with the minimal temperature reached (**Tab. 2**). There was a trend towards increased incidence of coagulation problems (both lab and clinical) for infants who had registered temperatures below 32.0ºC. The conclusions are, of course, hampered by the retrospective design and by the small number of infants studied.

In our study there was no statistically significant association between birth weight and the risk of excessive hypothermia.

Discussion

The use of properly designed clinical protocols for initiation and maintenance of passive hypothermia can help to achieve TH, while avoiding the potential risks associated with overcooling.

The delays in contacting the referral center (46% after the first hour) and beginning of passive cooling (19% started between 1 and 6 hours) occurred mostly during the first year. Although information was initially given to most referring hospitals and many training sessions were promoted at those hospitals, we think that the introduction of a new treatment was associated with delayed acknowledgement of treatment indications and timings. This is reflected in our results. Some changes occurred in the neonatal transport team during the study period. Initially clear recommendations were given by the attendant neonatologist to the referring hospital and transport team, but a specific protocol for transporting patients to TH was progressively implemented during the first year. We plan to reassess transport data in the future to evaluate eventual improvements after more than 5 years of experience in the transport of these infants.

As we could not detect any link between excessive hypothermia on arrival at NICU and the

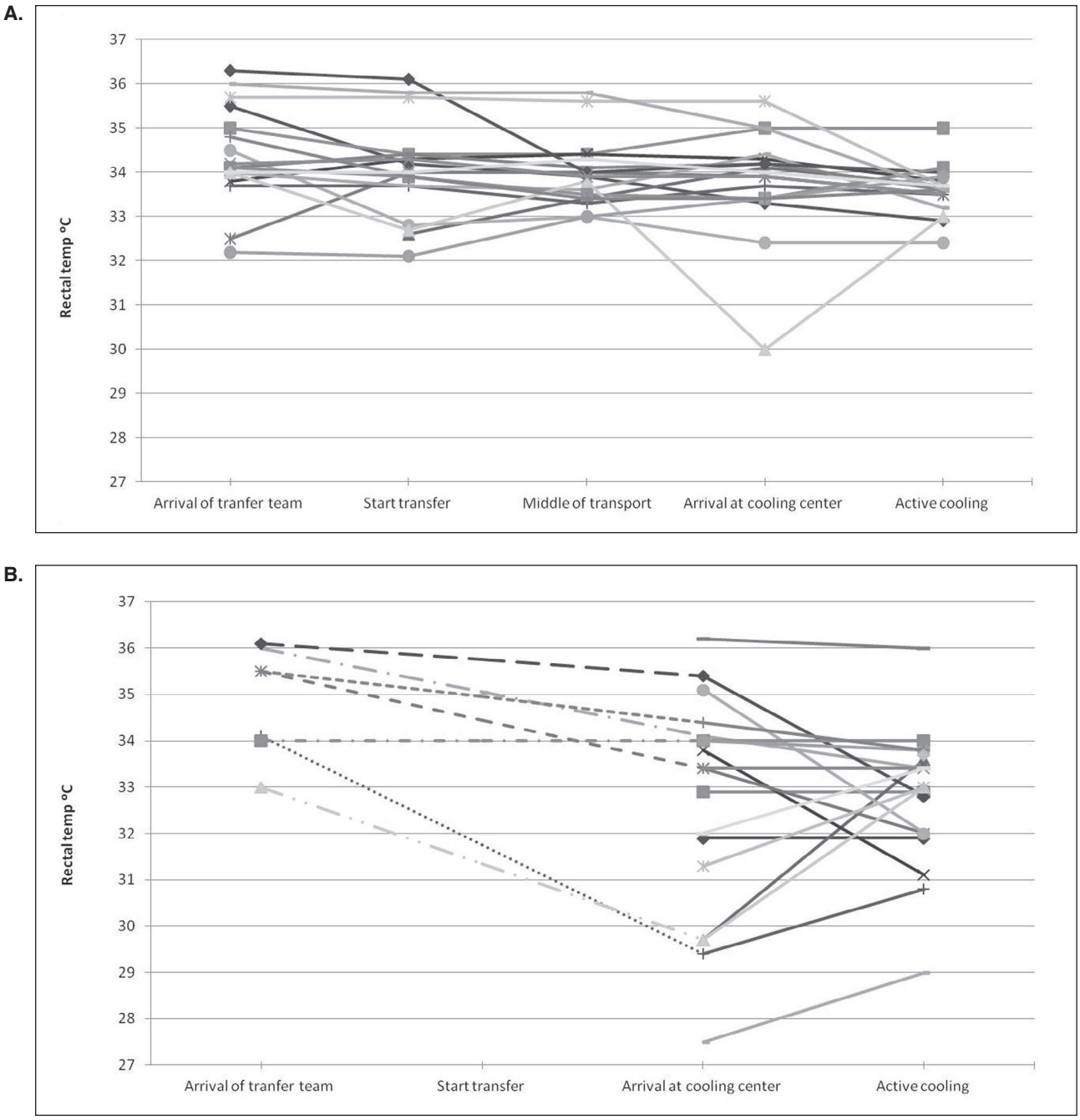

Figure 3. Comparison of individual temperature records between patients with: **A**) Adequate transport data; **B**) inadequate transport data. Dashed lines represent the period in which no record was available.

distance travelled or the time spent in transport, we can infer that strict application of the transport guidelines allows long distance transportation with minimal risk, even when not using a servo-controlled cooling device. A significant number of infants transported from nearer referring hospitals and with shorter transport times arrived to the center with excessive hypothermia, and this could be linked to the absence of adequate temperature records. Thus, it should be emphasized that rigorous temperature monitoring should be applied in all situations, including short distance transport.

Efforts to educate health care providers [8], development of guidelines and transport protocols [10] and increased experience of cooling during transport will likely improve results [16].

Our findings support the need for continuous monitoring of central body temperatures during initial stabilization and transport on passive hypothermia, starting as soon as active warming measures are turned off, in order to allow early

Table 1. Temperature of the group with adequate transport records (A) and without adequate transport records (B) at different timings.

		Group A	Group B
Number of patients		18	19
Arrival of transfer team	**Normothermia**	22%	21%
	Neuroprotective temperature	61%	16%
	Excessive hypothermia	11%	0%
	No records	6%	63%
Arrival at hypothermia centre	**Normothermia**	6%	16%
	Neuroprotective temperature	83%	37%
	Excessive hypothermia	11%	42%
	No records	0%	5%
Considering all measurements	**At least once excessive hypothermia**	39%	63%
	Experienced temperatures ≤ 32.0°C	6%	53%

Normothermia: 35.1º-36.9ºC; neuroprotective temperature: 33.0º-35.0ºC; excessive hypothermia: < 33.0ºC.

Table 2. Relation between the minimum temperature achieved and the incidence of complications.

	< 31.0ºC	31.0-31.9ºC	32.0-32.9ºC	33.0-37.0ºC
Number of patients	5	6	8	11
Seizures	100%	50%	75%	82%
Hypotension	80%	67%	75%	55%
Coagulopathy	60%	50%	13%	27%

attainment of a neuroprotective temperature while avoiding excessive hypothermia. This is demonstrated in the comparison of the two groups depicted in **Fig. 3**. Absence of adequate temperature records during transport is statistically associated to a higher risk of achieving temperatures below 33.0ºC on arrival (**Tab. 1**).

Infants arriving to the NICU with excessive hypothermia should be rewarmed slowly until they achieve a safe neuroprotective temperature [11].

We found no significant difference in the incidence of complications, including seizures, hypotension and coagulopathy, between different temperatures on arrival to our NICU, and these findings are consistent with those described by Compagnoni et al. [17]. Nevertheless, we did find a trend towards increased incidence of coagulation problems (both lab and clinical) in infants who had registered temperatures below 32.0°C, supporting the theoretical risks of increased incidence of coagulation problems during hypothermia. While waiting for more data from further investigations, these findings should be taken into account as they stress the importance of implementing rigorous temperature monitoring during transport in passive hypothermia. This monitoring will allow early but safe attainment of neuroprotective temperature in infants referred to TH.

Abbreviations

HIE: hypoxic-ischemic encephalopathy
NICU: neonatal intensive care unit
TH: therapeutic hypothermia

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Declaration of interest

The Authors declare no conflicts of interest. No specific funding was obtained for this study.

Ethical standards

The study was approved by the Medical Ethical board of Santa Maria Hospital – Lisbon Academic Medical Center.

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