Evaluating a Simple Method of Neuroprotective Hypothermia for Newborn Infants

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Summary
This study describes and evaluates a simple method of neuroprotective hypothermia for infants with hypoxic-ischaemic encephalopathy (HIE). Five term infants with HIE were cooled by applying soft, cold gel bags to the head. A radiant warmer, set to 34°C, servo-controlled the temperature measured at a probe between the infant’s back and the mattress. The infants’ heads were shielded from the warmer. After 72 h, the infants were re-warmed by 0.2°C per hour, by adjusting the radiant warmer. A rectal temperature of 34°C was attained in a median time of 45 min. Mean rectal temperatures during cooling were 33.9±0.3°C. There was good correlation between insulated back temperatures and deep rectal temperatures (r=0.76). There were no major or irreversible adverse events during cooling. This method of cooling achieved rectal temperatures within the target range of 33–34°C and re-warming was effective.

Key words: newborn infant, therapeutic hypothermia, hypoxia-ischaemia, developing countries.

Introduction
In well-resourced settings, therapeutic hypothermia is increasingly being recommended for newborn infants with moderate or severe hypoxic-ischaemic encephalopathy (HIE) [1–3]. Two randomized controlled trials [4, 5] and three systematic reviews [6–8] concluded that hypothermia to a brain temperature of 33–34°C, commenced within 6 h of birth, and maintained for 72 h, significantly reduced death or severe disability in this group of infants. International consensus statements [9, 10] suggest that therapeutic hypothermia for newborns with HIE should only be offered if the methodology follows the established protocols described in published studies, but the cooling equipment used in these studies is expensive, it has only recently become available in South Africa, and it requires specialized training. The use of therapeutic hypothermia in resource-limited settings is still considered experimental [11]. Although many hospitals in South Africa have neonatal intensive care facilities, the staffing shortages and budget limitations have prompted further research into simple, inexpensive cooling methods. Mowbray Maternity Hospital (MMH) is a level-2 regional maternity hospital where a basic method of neuroprotective hypothermia was described in 1999 [12]. The encouraging short-term outcomes from that study and the accumulating evidence of benefit from hypothermia [4, 5] led to the continued use of a modified method. Before the modified method could be considered in further prospective studies and similar resource-limited settings, the efficacy of the method had to be evaluated further.

We planned to evaluate the efficacy of the method in five term infants. We aimed to determine if target rectal temperature was achieved within an acceptable time, to determine if rectal temperatures were

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maintained in an acceptable range, and to determine if the method of monitoring the skin temperature between the skin and the mattress is a suitable alternative to direct rectal temperature monitoring.

**Methods**

This study was done in the Neonatal Unit of MMH, a satellite teaching hospital of the University of Cape Town, South Africa. The study was approved by the Human Research Ethics Committee and conformed to the principles of the Declaration of Helsinki [13].

Temperature data was collected prospectively on five infants that were being cooled according to the existing standard of care at MMH. The only intervention additional to the existing standard of care in these infants was the monitoring and logging of rectal temperatures at two additional skin sites. Informed consent for data collection and publication of images was obtained from the mothers of the infants.

At MMH infants receiving neuroprotective hypothermia were required to meet the following criteria:

- a) Gestational age of 36 or more weeks and weight ≥ 2000 g;
- b) Less than 6 h old at initiation of hypothermia;
- c) Signs of HIE and seizures or voltage suppression on aEEG as defined by al Naqeeb et al. [14] or if HIE was clinically severe or seizures were clinically evident then aEEG criteria were not required;
- d) Base deficit of 16 or more in the first hour of life on cord or infant arterial blood; or 10 min Apgar score of <7 or requiring some form of assisted ventilation at age 10 min plus an obstetric history suggestive of intrapartum hypoxia.

Infants were not cooled if any of the following were present: major congenital abnormalities, active bleeding, obvious sepsis, persistent pulmonary hypertension requiring Fractional inspired oxygen (FiO2) above 0.8 to maintain oxygen saturation of 94%, or if there was severe hypoglycaemia or electrolyte abnormality that did not respond to usual therapy.

Hypothermia was achieved by applying one or two soft, 12 × 12 cm, 250 g gel bags (Penguin Manufacturers, International Health Care Distributors) around the head, and controlling the core body temperature with a servo control radiant warmer (Servocrib, Servocare Medical Industries cc, Cape Town, South Africa) set at a target temperature of 34°C. This is the lowest target temperature that the warmer is capable of. The bags were stored in a refrigerator kept at 7–10°C and were replaced hourly when routine observations were done. The core temperature was measured and controlled using a temperature probe between the infant and the mattress. This method of core temperature measurement has been ratified in similar cooling studies [15].

A reflective perspex heat-shield was placed over the head to prevent facial heating by the radiant warmer. If the infant core temperature was below 33°C, then the bags were removed for an hour. If the infant core temperature was above 34.5°C, then further bags were added around the upper body. Infants were sedated with intravenous morphine at 8 µg/kg/h unless they were sufficiently sedated with anticonvulsants.

A rectal temperature probe was inserted 4–5 cm into the rectum and two additional skin probes were attached to the surface abdomen over the left upper quadrant and to the middle of the back. These latter two probes were insulated with adhesive reflective coverings. Ambient temperature was monitored by means of a fourth probe attached to the side of the radiant warmer. The probes were connected to a dedicated data logger (Squirell 2010, Grant Instruments, Cambridge, UK) which logged temperature at these sites every 15 min for the duration of cooling.

After 72 h of cooling, infants were re-warmed by removing the bags and increasing the target temperature on the radiant warmer by 0.2°C every hour until attaining 36.5°C. Then the heat-shield was removed and the core temperature was subsequently maintained at 36.5–37°C until the infant was well enough to be transferred to a bassinette.

Infants received routine monitoring of vital signs, acid base parameters, electrolytes, haematological parameters and sepsis indicators. Clinical seizures and subclinical status were treated with up to two loading doses of intravenous phenobarbital 20 mg/kg and thereafter by midazolam infusion, followed by lignocaine infusion for refractory seizures. A Thompson neurological assessment [16] was performed daily for the first 10 days and aEEG monitoring was continued for 96 h or until normal background was present for 24 h.

**Results**

Four infants had a history of bradycardia during labour and one infant had a history of meconium-stained liquor. Arterial blood gas analysis in the first hour of life was available in three infants and the base deficit ranged from 15.9 to 19.5. The other two infants were out-born but were still requiring assisted ventilation at age 10 min. Table 1 shows the clinical characteristics of all the infants. The median birth weight was 3060 g, the median 5-min Apgar score was five and the median age of onset of cooling was 5.5 h. Two infants were assessed as Sarnat grade 3, two others were assessed as grade 2, and one infant was assessed as grade 1. Cooling was commenced within a median time of 5.5 h. The onset of cooling was delayed by the process of stabilizing the infant after birth and placing the aEEG sensors. Two infants were admitted to the unit after age 3 h.
Table 2 shows the temperature variation. A rectal temperature of 34°C was attained within a median time of 45 min from commencement of cooling. The back temperature tended to read 0.1–0.5°C higher than the rectal temperature at the time target temperature was attained, but subsequently the mean difference between the rectal and back temperatures was 0.1°C. The mean rectal temperature during cooling was 33.9°C ± 0.3°C in a mean ambient temperature of 24.6°C ± 0.5°C.

Figure 1 further shows the close correlation between rectal and insulated back temperatures in the entire group and Fig. 2 shows a single case, demonstrating the correlation between rectal and back temperatures and the wide variation in the surface abdominal temperatures from 32.2 to 36.3°C. This case also demonstrates the ease and accuracy of re-warming the infant by increasing the radiant warmer target temperature by 0.2°C per hour, whilst retaining the heat-shield in place.

Figure 3 shows the rectal temperatures of all infants and demonstrates that the rectal temperatures remained at or below 34°C for the majority of the time.

There were very few adverse events during cooling. All infants had a physiological sinus bradycardia of <100 beats per minute, but only two infants required inotropes. Although the maximum creatinine ranged from 92 to 144 μmol/l (median 103), there were no electrolyte abnormalities. One infant had transient hypoglycaemia and one infant had transient pulmonary hypertension that resolved without the need for nitric oxide.

All infants survived to discharge. Three infants were sucking well enough to be discharged by Day 10, despite the fact that two of these infants had severe suppression on aEEG on recruitment. Enteral feeding at a volume of 80 ml/kg/day was achieved by a median of 4 days (range 4–7 days).

Discussion

We have shown that hypothermia may be successfully achieved in term infants with HIE, simply by reducing the target radiant warmer temperature to 34°C, covering the infant’s head with a heat shield and by applying soft gel packs around the head at a starting temperature of 7–10°C. We have also confirmed that a temperature measured at a point

<table>
<thead>
<tr>
<th>Infant</th>
<th>Ambient temperature during cooling (°C) ± SD</th>
<th>Rectal temperature before cooling (°C) ± SD</th>
<th>Intracool® rectal temperature (°C) ± SD</th>
<th>Intracool® back temperature (°C) ± SD</th>
<th>Time to reach rectal target (34°C) (min)</th>
<th>Back temperature when rectal target was reached (°C) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24.6 ± 0.5</td>
<td>35.7</td>
<td>33.9 ± 0.3</td>
<td>33.9 ± 0.3</td>
<td>30</td>
<td>34.5</td>
</tr>
<tr>
<td>2</td>
<td>23.7 ± 0.5</td>
<td>35.1</td>
<td>34.0 ± 0.2</td>
<td>34.1 ± 0.4</td>
<td>45</td>
<td>34.5</td>
</tr>
<tr>
<td>3</td>
<td>24.0 ± 0.5</td>
<td>36.1</td>
<td>33.9 ± 0.2</td>
<td>33.8 ± 0.3</td>
<td>60</td>
<td>33.9</td>
</tr>
<tr>
<td>4</td>
<td>26.5 ± 1.5</td>
<td>36.2</td>
<td>33.9 ± 0.2</td>
<td>33.8 ± 0.2</td>
<td>30</td>
<td>34.4</td>
</tr>
<tr>
<td>5</td>
<td>24.3 ± 0.4</td>
<td>34.7</td>
<td>33.7 ± 0.2</td>
<td>33.7 ± 0.2</td>
<td>45 (median)</td>
<td>34.4 (median)</td>
</tr>
<tr>
<td>All</td>
<td>24.6 ± 0.5</td>
<td>35.7 (median)</td>
<td>33.9 ± 0.3</td>
<td>33.9 ± 0.4</td>
<td>45 (median)</td>
<td>34.4 (median)</td>
</tr>
</tbody>
</table>

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Figure 3 shows the rectal temperatures of all infants and demonstrates that the rectal temperatures remained at or below 34°C for the majority of the time.

Table 1

<table>
<thead>
<tr>
<th>Infant</th>
<th>Weight (g)</th>
<th>5 min Apgar</th>
<th>aEEG suppression at recruitment</th>
<th>Seizures</th>
<th>Age cooling started (h)</th>
<th>Anticonvulsant and opiates</th>
<th>Inotrope</th>
<th>Ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2700</td>
<td>6</td>
<td>Severe (FT)</td>
<td>Subtle + ESz</td>
<td>6</td>
<td>Phenobarbital</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>3600</td>
<td>3</td>
<td>Severe (CLV)</td>
<td>Subtle</td>
<td>3</td>
<td>Phenobarbital</td>
<td>No</td>
<td>MV/NCPAP</td>
</tr>
<tr>
<td>3</td>
<td>3640</td>
<td>4</td>
<td>Moderate (DNV)</td>
<td>Tonic + ESz</td>
<td>5.5</td>
<td>Phenobarbital</td>
<td>Yes</td>
<td>MV/NCPAP</td>
</tr>
<tr>
<td>4</td>
<td>2800</td>
<td>6</td>
<td>Moderate (DNV)</td>
<td>None</td>
<td>5.5</td>
<td>Morphine</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>3060</td>
<td>5</td>
<td>Severe (FT)</td>
<td>Subtle + ESz</td>
<td>4.25</td>
<td>Phenobarbital Midazolam</td>
<td>No</td>
<td>Nasal canulae</td>
</tr>
</tbody>
</table>

DNV: Discontinuous normal voltage, CLV: Continuous low voltage, FT: Flat trace, ESz: Electrical seizures, MV: Mechanical ventilation, NCPAP: Nasal continuous positive airway pressure.

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that is insulated between the mattress and the body accurately reflects a core temperature in this setting.

Similar methods of inducing hypothermia have been used in other studies [17, 18], but in those studies, the radiant warmer was adjusted manually and the rectal temperature was measured directly. Manual temperature adjustments are more labour-intensive and require greater skill than our method of hourly bag changes.
The methodology used in our study is simpler and less expensive than the cool cap or mattress cooling methods described in the two largest randomized controlled studies published to date [4, 5]. Four of the five infants in our study achieved a rectal temperature of 34°C by 60 min or less, compared to average cooling times of 120 and 90 min, using the more expensive methods described above. Although only five infants were cooled, a total of 1248 temperatures were measured during cooling and the standard deviation (SD) of ±0.3°C shows good temperature stability.

The infants’ heads were shielded during cooling and re-warming to prevent excessive facial and scalp heating which has been described in infants nursed under radiant warmers [19]. The facial vein drains via the ophthalmic vein to the cavernous sinus and hence heating of the face may cause relative heating of the base of the brain. It is similarly important to use lower humidifier temperature settings than usual when ventilating cooled infants. The humidifier used in the two infants who required ventilation (MR 850, Fisher and Paykel, New Zealand) was set at the lower of the two automated options, which resulted in the distal sensor reading of 34–35°C.

Insulated skin temperature monitoring as the primary temperature control point is standard at MMH due to ease of application. Studies in piglets [20], preterm infants [21] and term infants nursed in closed incubators [15], demonstrated the zero gradient principle where a point insulated between body and mattress will equilibrate to the warmest part of the body. The good correlation between the insulated back temperature and the rectal temperature in our study including 1248 temperatures, confirms that this type of monitoring is reasonable.

Although the rectal temperatures achieved in this study were in the higher end of the range of cerebral neuroprotective temperatures, the regular application of gel bags when rectal temperatures were above 33.5°C may have decreased the scalp temperature sufficiently to achieve further mild cortical cooling. However, our method must be distinguished from uniform selective cerebral cooling [4] where rectal temperature is maintained at 34–35°C and the constant low scalp temperature results in consistently lower brain temperatures.

Sedation during cooling is recommended [22–24] and we used intravenous morphine at low doses, to provide sedation to infants who did not require anticonvulsants, or who were not sufficiently sedated despite anticonvulsants. The morphine at the doses we used did not cause apnoea but it may have enhanced the hypothermia [25].

Since completion of our study, a very basic method of cooling using hot water bottles filled with tepid tap water achieved good temperature control [26] if blankets were added intermittently to prevent excessive hypothermia. The infants were nursed in simple cots in a setting with limited electricity and no air-conditioning, which is very different to our setting.
Conclusion

This simple method of inducing and maintaining hypothermia achieved stable rectal temperatures within an acceptable time and the insulated back temperatures correlated well with rectal temperatures. The intervention was well defined and simple. This approach makes therapeutic hypothermia immediately accessible at virtually no cost. The method may be particularly suited to level-2 units with infants awaiting transfer and it might also be considered as a method of cooling in further trials. Currently, most models of radiant warmers and incubators do not permit a target temperature below 34°C. If radiant warmers that allow a target temperature of 33.5°C are used then deeper cooling would probably be easily maintained using the same simple method.

References