Selective cerebral hypothermia for post-hypoxic neuroprotection in neonates using a solid ice cap

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Objective. The main objective of this study was to study the safety and efficacy of a simple, cost-effective method of selective head cooling with mild systemic hypothermia in newborn infants with hypoxic ischaemic encephalopathy.

Design. Ethical approval was obtained for a randomised controlled study in which 20 asphyxiated neonates with clinical signs of hypoxic ischaemic encephalopathy would be randomised into cooled and non-cooled groups. However, after cooling the first 4 babies, it was clear that repeated revisions to the cooling technique had to be made which was inappropriate in the context of a randomised controlled trial. The study was therefore stopped and the data for the 4 cooled infants are presented here in the form of a technical report. Hypothermia was achieved by applying an insulated ice cap to the heads of the infants and replacing it at 2 - 3-hourly intervals, aiming to achieve a target rectal temperature of 35 - 35.5°C and a target scalp temperature of 10 - 28°C.

Setting. This study was carried out between July 2000 and September 2001 in the neonatal units of Groote Schuur Hospital and Mowbray Maternity Hospital, Cape Town.

Subjects. Term infants with signs of encephalopathy were recruited within the first 8 hours of life if they had required resuscitation at birth and had significant acidosis within the first hour of life.

Results. Target rectal temperature was achieved in all infants, but large variations in incubator and scalp temperatures occurred in 3 of the 4 infants. Reducing the target core temperature in a stepwise manner did not prevent excessive temperature variation and resulted in a longer time to reach target temperature. There was least variation in scalp temperature when the ice pack was covered in two layers of mutton cloth before application, but the resulting scalp temperatures were above the target temperature. The maximum scalp temperature variation was reduced from 22°C to 12°C using this method. Nasopharyngeal temperatures varied excessively within less than a minute, suggesting that air cooling via mouth breathing was occurring. The surface site that correlated best with deep rectal temperature was the back, with the infant supine. During cooling, the respiratory rate and heart rate dropped while the mean arterial blood pressure was elevated. There were no irreversible adverse events due to cooling, but infants did become agitated and exhibited shivering which required sedation and analgesia.

Conclusions. Nasopharyngeal temperature monitoring was not reliable as an acute clinical indicator of brain temperature in these spontaneously breathing infants, and the back temperature in supine infants correlated better with deep rectal temperature than did exposed skin temperature. This method of cooling achieved systemic cooling but there were large variations in regional temperatures in 3 of the 4 infants. The variations in temperature were probably due to the excessive cooling effect of the ice cap, coupled with the use of external heating to maintain systemic temperature at 35 - 35.5°C. Variation in temperature was reduced when additional insulation was provided. However, the additional insulation resulted in the loss of the selective cerebral cooling effect. This cooling technique was therefore not an appropriate method of selective head cooling, but did successfully induce systemic hypothermia. This method of insulating an ice cap could therefore be used to induce whole-body cooling but the use of lower core temperatures of 33 - 34°C is recommended as this will probably result in fewer regional temperature fluctuations. Ideally a more uniform method of cooling should be used.

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Hypoxic ischaemic insults during labour remain an important cause of brain injury in term and near-term infants.[1] Brain injury that occurs in this way is an evolving process and the clinical manifestation of this injury is termed hypoxic ischaemic encephalopathy (HIE).[2]

Several animal studies have shown that the evolving brain injury in newborn animals following a hypoxic ischaemic insult is potentially amenable to neuroprotective rescue therapy in the form of cerebral hypothermia.[3-7] Focal cerebral cooling, with mild systemic cooling, achieves neuroprotection with fewer systemic complications than deep whole-body cooling.[8,9]

In 1998, Gunn *et al.*[10] published a safety study using a cooling coil that circulated water at 10°C around the head. The scalp temperature of the cooled infants fell to 28°C and the rectal temperature was 35.7 ± 0.2°C. In this study, no significant adverse effects of cooling were detected if the core temperature was maintained above 34.2°C. Following the initial safety

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study by Gunn *et al.*,[10] we sought to devise a simpler form of head cooling that could be used in developing countries.

Ice packs have been applied to the heads of neonates during cardiopulmonary bypass surgery[11] and cooling caps at -30°C, covered in cloth, were applied to piglets' heads after cardiac arrest and resuscitation, with no local complications.[12] We therefore designed this study to pilot a simple insulated ice pack, aiming for similar temperatures to those described by Gunn *et al.*[10]

A study of asphyxiated fetal sheep found that prolonged cerebral cooling started within 5.5 hours of birth is associated with neuronal rescue, but delaying the rescue to 8.5 hours results in a loss of the effect.[8] Therefore, we recruited infants as early as possible, but set 8 hours as the maximum recruitment age.

Ethical approval was obtained from the University of Cape Town Medical Research Ethics Committee to conduct a randomised controlled study of selective cerebral hypothermia on 20 infants with HIE. However, after cooling the first 4 babies, it was clear that repeated revisions to the technique had to be made and that the ice cap was not a satisfactory method of inducing selective cerebral cooling. If selective cerebral cooling was not being achieved then lower core temperatures would have to be used in those infants. The study was therefore stopped and the data and observations from the 4 cooled infants are presented here in the form of a technical report.

Method

Setting

This study was done in the neonatal units of Groote Schuur Hospital and Mowbray Maternity Hospital, Cape Town, South Africa.

Patients

From July 2000 to September 2001, infants were recruited during the first 8 hours of life when they met the following entry criteria: a gestational age of 37 or more weeks, a base deficit of 10 or more on arterial cord blood (or infant's arterial blood within the first hour), an Apgar score of 6 or less at 5 minutes after birth or the need for assisted ventilation at delivery, and signs of encephalopathy (with a score of at least 2 on a previously validated scoring system).[13] Written informed consent was obtained from parents or legal guardians.

Exclusion criteria were major congenital abnormalities, active bleeding, obvious sepsis, hypoxaemia requiring more than 50% oxygen to maintain normal oxygen saturation and severe hypoglycaemia or electrolyte abnormality not responding to standard therapy.

Procedures

As soon as infants met the entry criteria, an insulated ice cap was applied and changed as required to maintain the rectal temperature (probe inserted 5 cm into the rectum) at 35 - 35.5°C and a scalp temperature of 10 - 28°C. All infants were nursed in a closed, non-humidified incubator (Airshields, C100).

Temperature was regulated by servo-controlling the back skin temperature on supine infants. This location was chosen because it should approximate the rectal temperature but is technically easier to access. Scalp temperature over the anterior fontanelle, and nasopharyngeal and surface abdominal skin temperatures were also monitored. The probe position for nasopharyngeal temperature monitoring was estimated by measuring the nostril to ear tragus distance but in all cases this resulted in the tip of the probe protruding past the uvula, so it was withdrawn until it was palpable immediately above the uvula.

The temperature probes used in all infants were disposable thermistor probes, equivalent to the Yellow Springs International 400 series (Respiratory support Products, Inc., Smiths Industries Medical Systems, California, USA). Soft silicone size 8 French Foley catheter temperature probes with the same specifications as above were used (not inflated) in the rectum and nasopharynyx. Abdominal skin probes were fixed in position with a reflective disc supplied by the manufacturer and back skin and fontanelle probes were fixed in position using Tegaderm. Temperatures were documented every 5 minutes at all sites except the back temperature which was monitored every 2 hours.

The ice pack that was used for head cooling was a 12 × 12 cm freezable gel pack made by Penguin Manufacturers. This pack is normally used to keep vaccines cool in transit. The pack was covered with mutton cloth and then frozen around an empty 2-litre cooldrink bottle to obtain a suitable curvature. The frozen ice pack was then secured onto the baby's head over the anterior fontanelle.

Following severe fluctuations in incubator and scalp temperatures in the first case (Fig. 1), the optimal timing and method of placement of the ice cap was refined with each subsequent case as shown in Table I.

Restlessness and shivering were noticed in the first case treated. In the subsequent cases, phenobarbitone 20 mg/kg was routinely administered for sedation with the onset of cooling. If discomfort persisted, a second dose of phenobarbitone was administered and if discomfort persisted further, then morphine 0.03 mg/kg was given as a slow intravenous bolus. Apart from the cooling and additional sedation and analgesia, all infants received standard clinical care.

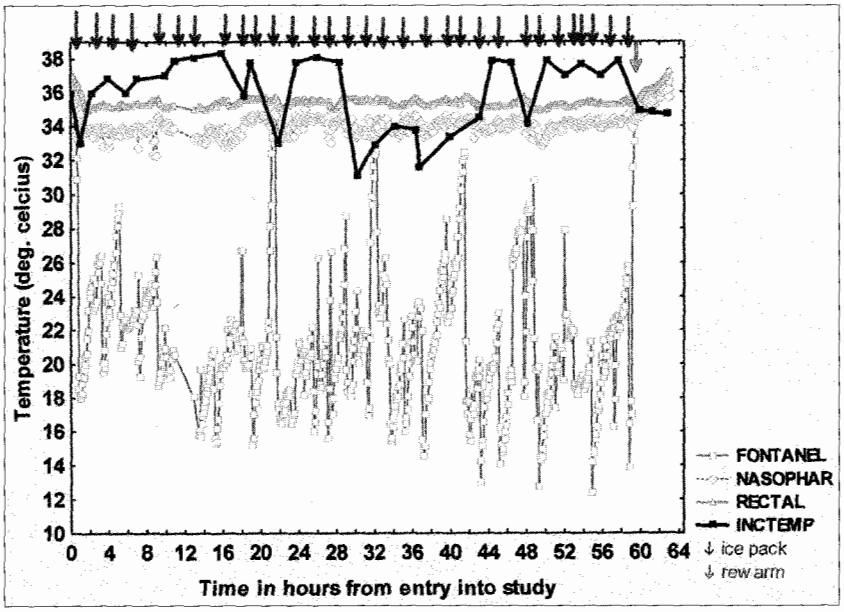

Fig. 1. Temperature variation during cooling in case 1.

Intravenous fluids were provided using potassium-free Neonatalyte at an initial volume of 50 ml/kg. Fluids were then adjusted on a daily basis as judged by the attending paediatrician. Clinical seizures occurred in 1 patient only and these were controlled with a second dose of phenobarbitone 20 mg/kg.

Cooling continued for 72 hours or until the encephalopathy had resolved, but the minimum duration of cooling was 48 hours.

Statistical analysis

Temperature and vital signs data were analysed and graphically displayed using Statistica 6.0.

Results

Baseline characteristics

Birth weights ranged from 2 730 g to 3 100 g and the base deficit in the first hour of life ranged from 12 to 16.5. Cerebral ultrasound was suggestive of cerebral oedema in 3 of the 4 infants at recruitment, but no infant manifested clinical seizures before cooling and all infants were breathing spontaneously in room air at the time.

Table I. Cooling and re-warming strategies in the 4 cooled infants*

	Case 1	Case 2	Case 3	Case 4
Age cooling commenced	5:24	5:50	5:30	7:20
Empiric phenobarbitone pre-cooling	No	Yes	Yes	Yes
Layers of cloth over ice pack	1	1	1	2
Reflective covering over ice cap	No	Yes	No	No
Ice cap change interval	2-hourly	2-hourly	2-hourly	3-hourly
Induction of cooling protocol when ice cap is first applied	Servo-control back temperature to 35.5°C	Servo-control back temperature to 36.5°C for 10 minutes, then reduce by 0.2°C every 15 minutes until 35.5°C	Servo-control back temperature to 35.2°C	Servo-control back temperature to 36.5°C and reduce by 0.2°C every half hour until 35.3°C
Time to reach target rectal temperature	00:45	2:00	4:00	3:00
Duration of cooling	59:20	72:00	71:05	72:05
Warming protocol from the time of removing ice cap	Servo-control back temperature to 36°C then increase by 0.5°C hourly until 37°C	Servo-control back temperature to 35.5°C for 1 hour. Increase by 0.5°C after 1 hour, then by 0.2°C per hour until 37°C	Servo-control back temperature to 35.2°C for 15 minutes, then increase to 35.5°C and continue to increase by 0.5°C per 30 minutes until 37°C	Servo-control back temperature to 35.5°C for 1 hour. Increase to 36.5°C after 1 hour and increase to 37°C after another hour
Duration of re-warming	3:00	7:00	4:00	2:00

*Time shown as hours: minutes.

Regional temperature variation

The target rectal temperature of 35 - 35.5°C was achieved in all cases except case 3 in which the mean rectal temperature was 34.7°C. The only case with an acceptably short time to target rectal temperature of under 1 hour was case 1. The rapid head cooling in this case and case 3 resulted in high incubator temperatures. The longer cooling time in case 3 was the result of manual manipulation of the incubator settings.

The incubator temperature varied by up to 7°C in cases 1 and 3 and by up to 9°C in cases 2 and 4, but in cases 1 and 3, the incubator temperature rose above 37°C on several occasions. Fig. 1 shows the excessive regional temperature variations experienced by case 1 and this is representative of all cases, except case 4, where the maximum scalp temperature variation was reduced from 22°C to 12°C. The incubator temperature in this case only rose above 36°C to 36.5°C on one occasion.

The target scalp temperature was achieved in all infants except in case 4 where the mean nasopharyngeal temperature was 29.7°C. The use of a reflective covering on the ice cap in case 2 prevented adequate monitoring of the ice cap position and did not prevent incubator temperature fluctuation. Rewarming occurred in all infants in proportion to the speed with which the external heating was increased; the fastest rewarming time of 1°C per hour was achieved by increasing the desired temperature by the same rate, as was done in case 4.

Nasopharyngeal temperature monitoring

Although the trend of nasopharyngeal temperatures represented graphically in Fig. 1 suggests an increased nasopharyngeal-rectal temperature gradient during cooling, individual nasopharyngeal temperatures fluctuated rapidly and by several degrees over less than a minute in infants during times of agitation and rapid mouth breathing or crying.

Back temperature (in supine infants) versus surface abdominal temperature

Data from the 4 cooled infants were used to correlate insulated back temperatures and surface abdominal temperatures with rectal temperatures (Figs 2 and 3). The insulated back temperatures correlate much better with rectal temperatures than did the surface abdominal skin temperatures.

Cardiovascular and respiratory observations

The data of all groups were analysed collectively. During cooling, the respiratory rate dropped by an average of 19 breaths per minute, the heart rate dropped by an average of 17 beats per minute, and the mean arterial blood pressure rose by an average of 6 mmHg. During rewarming, these parameters returned to the precooling state and at no time were the infants compromised by these changes.

Biochemical and haematological complications during cooling

Biochemical and haematological monitoring showed no significant irreversible adverse events due to cooling. In case 1, the serum sodium dropped to 125 mmol/l on day 2 and blood sugar rose to 18 mmol/l because of inadvertent administration of excess intravenous fluid. Hypokalaemia was not encountered. Case 3 had transient hypoglycaemia. The metabolic acidosis on admission to the study progressively resolved during cooling and renal failure did not occur. The maximum prothrombin index of 2.5 on day 2 improved to normal limits by day 4 after treatment with intravenous vitamin K. No infant acquired infection during or after the study period.

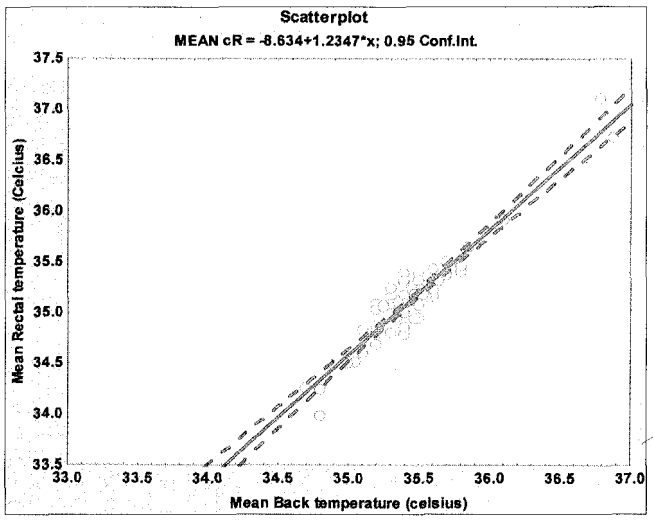

Fig. 2. Mean rectal temperature versus mean back temperature during cooling.

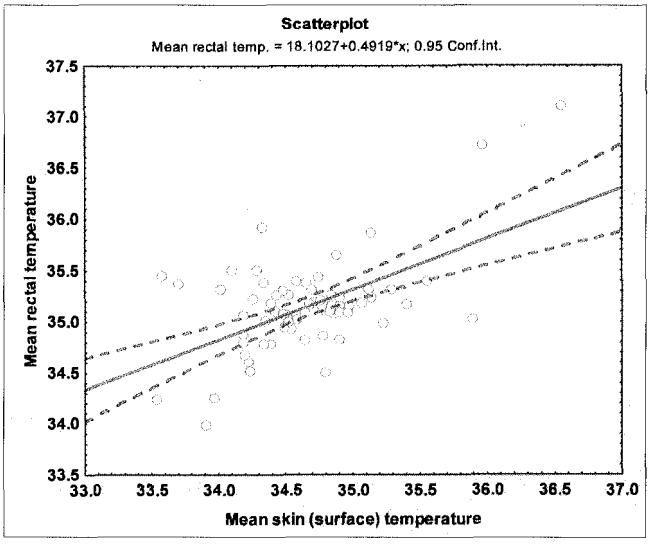

Fig. 3. Mean rectal temperature versus mean surface abdominal skin temperature during cooling.

Physical and short-term neurological outcomes in cooled infants

There were no local side-effects from the ice packs. Two of the cooled infants progressed to moderate encephalopathy but there were no neurological abnormalities at the time of discharge in any of the infants. Full feeds were established between day 5 and day 8.

Discussion

This method of cooling is not simple and there were large fluctuations in regional temperatures. The constant vigilance required to prevent further variation in incubator temperature and the repeated changing of the ice packs was labour intensive. The high incubator temperatures were thought to be due to the excessive cooling effect of the ice cap, coupled with the use of external heating to maintain systemic temperature at 35 - 35.5°C. The strategy of insulating the pack, making it less cool and at the same time prolonging the thaw time, resulted in lower incubator temperatures and less scalp temperature fluctuations but average scalp temperatures were higher than desired. Fluctuations in scalp temperature will not be noticed if scalp temperature is not measured frequently. This is an important finding because large variation in temperature causes variable perfusion and this could potentially exacerbate cerebral injury.

Although the exact depth of cooling required to achieve neuroprotection is not known, a review of several studies14 suggests that the optimal brain temperature to achieve neuroprotection with minimal side-effects is 32 - 34°C. Brain temperature during cooling has been related to scalp temperature using numerical modelling15 which predicts that a scalp temperature of 24°C with a core temperature of 34°C results in a temperature gradient of 32 - 28°C across the cortex. Therefore, in the first two cases with mean scalp temperatures of 21°C, there was probably significant selective cerebral cooling, but the scalp temperatures of 27 and 29.7°C in cases 3 and 4 respectively, suggest that selective cerebral cooling was not achieved in these cases. If significant selective cerebral cooling is not occurring, then deeper core temperatures of 33 - 34°C must be achieved with whole-body cooling.

Gunn *et al.*[10] used nasopharyngeal temperatures to infer cerebral cooling. However, we found that the nasopharyngeal temperature varied greatly with mouth breathing and therefore has little value in spontaneously breathing infants.

Gunn *et al.*[10] used surface abdominal skin as a site to servo-control temperature of cooled infants but commented that manual adjustment was required intermittently. We also found that the surface abdominal temperature varied greatly and was subject to environmental influence. The covered back temperature showed close correlation with the rectal temperature and in future studies we suggest that this site could be used to servo-control temperature instead of rectal temperature.

The infants that we cooled frequently became agitated and exhibited shivering. In animal studies, unsedated cooled piglets had cortisol levels three times higher than those of their normothermic counterparts16 and neuroprotection was not successful. This supports our finding that sedation and analgesia are necessary during induced hypothermia.

In summary, the salient lessons and recommendations that can be derived from the four infants studied are as follows:

1. Solid ice cap application is not recommended for inducing selective cerebral hypothermia. Increased insulation of the ice cap can be used to successfully induce whole-body cooling but the fluctuation in incubator and scalp temperatures is still not ideal. However, there will probably be less fluctuation if external heating is reduced by accepting a target core temperature of 33 - 34°C which has recently been shown to be safe.17-19 A more uniform method of head or whole-body cooling would be preferable if it were available and simple to use.
2. The ice cap did not result in local complications.
3. Mild systemic cooling did not result in significant systemic or biochemical complications.
4. Nasopharyngeal temperature monitoring is not an accurate reflection of brain temperature in spontaneously breathing infants.
5. The superficial abdominal skin temperature was not a reliable indicator of core temperature, but the covered back temperature closely follows the core temperature and this site may be used as a less invasive alternative to deep rectal temperature monitoring.
6. Sedation and analgesia to control discomfort should be given to infants with induced hypothermia to reduce stress and decrease shivering.

The current international consensus opinion of the National Institute of Child Health and Human Development recommends that results from outstanding trials should be awaited and reviewed before hypothermia becomes a standard of care for infants with HIE, and that care should be taken to prevent inadvertent overheating of these infants.20 We support this statement. If infants with HIE are cooled, parental consent should be sought and there should be a careful audit of the intervention, bearing the above lessons in mind.

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