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Olympic Cool-Cap® Reference Bibliography

Author(s)	Title	Summary	Journal	Year	Vol:Pages
		COOL-CAP IN NEONATES			
Gluckman, P., Wyatt, J. S., Azzopardi, D., Ballard, R., Edwards, A.D., Ferriero, D.M., Polin, R. A., Robertson, C., Thoresen, M., Whitelaw, A., Gunn, A. J.	*Selective Head Cooling With Mild Systemic Hypothermia After Neonatal Encephalopathy: Multicentre Randomized Trial*	Background: Cerebral hypothermia can improve outcome of experimental perinatal hypoxia-ischaemia. We did a multicenter randomised controlled trial to find out if delayed head cooling can improve neurodevelopmental outcome in babies with neonatal encephalopathy. Methods: 234 term infants with moderate to severe neonatal encephalopathy and abnormal amplitude integrated electroencephalography (aEEG) were randomly assigned to either head cooling for 72 h, within 6 h of birth, with rectal temperature maintained at 34-35°C (n=116),or conventional care (n=118). Primary outcome was death or sever disability at 18 months. Analysis was by intention to treat. We examined in two predefined subgroup analyses the effect of hypothermia in babies with the most severe aEEG changes before randomization, i.e., severe loss of background amplitude, and seizures- and those with less sever changes. Findings: In 16 babies, follow-up data were not available. Thus in 218 infants (93%), 73/110 (66%) allocated conventional care and 59/108 (55%) assigned head cooling died or had severe disability at 18 months (odds ratio 0.61; 95% CI 0.34-1.09, p=0.1). After adjustment for the severity of a aEEG changes with a logistic regression model, the odds ratio for hypothermia treatment was 0.57 (0.32-1.01, p=0.05) No difference was noted in the frequency of clinically important complications. Predefined subgroup analysis suggested that head cooling had no effect in infants with the most severe aEEG changes (n=46, 1.8; 0.49-6.4, p=0.51), but was beneficial in infants with less severe aEEG changes (n=172, 0.42; 0.22-0.80, p=0.009). Interpretation: These data suggest that although induced head cooling is not protective in a mixed population of infants with neonatal encephalopathy, it could safely improve survival without severe neurodevelopmental disability in infants with less severe aEEG changes.	Lancet	2005	365:663-670
Bello, S.O. Dutta, S., Pradeep, G.C., Narang, A.	*Selective Head Cooling After Neonatal Encephalopathy*	Letter to Editor: Questions on analysis technique	Lancet	2005	365(9471):1619 365(9471):1619

Author(s)	Title	Summary	Journal	Year	Vol:Pages
Authors reply Alistair J Gunn	*Selective Head Cooling After Neonatal Encephalopathy*	As S.Dutta and colleagues note, we saw a chance bias in randomization so that more infants in the treatment group than the comparison group showed a very low 5-min Apgar score. This finding is also reflected in the fact that there were more infants with adverse modified Sarnat scores in the cooled group than in the control group. We chose not to include Apgar scores in the primary analysis because it is regarded by many as an imprecise measure of the severity of neonatal encephalopathy and a weak predictor of neurodevelopmental outcome. However, we agree that additional adjustment for illness severity might be informative, and we have therefore undertaken a further logistic regression analysis, which includes the Apgar and modified Sarnat scores as well as the aEEG background and presence of seizures. This analysis revealed a significant overall effect of hypothermia on the primary outcome of death or disability at 18 months (odds ratio 0·52, 95% CI 0·28–0·70, p=0·04) in the full study population (n=218). Consistent with previous reports, in this analysis the modified Sarnat score showed significant predictive value (stage 3 *vs* stage 1 or 2: 3·37, 1·64–6·93, p=0·001), 1–3 although the 5-min Apgar score did not (0·90, 0·76–1·06, p=0·21). As in earlier studies, the aEEG changes at randomization (seizures: 1·96, 1·02–3·74, p=0·04; background amplitude: 2·06, 1·01–4·17, p=0·05) and Sarnat score seem to be independently predictive. We speculate that clinical examination and aEEG recordings in the early hours after birth could provide complementary information on the severity of the perinatal insult and on how far advanced the process of injury was at the time of recruitment. Since the period from birth to enrolment varied little between infants, the stage of evolution of damage would mainly be influenced by the timing of intrauterine hypoxia. As Dutta and colleagues note, a prolonged period between hypoxia and treatment could be expected to reduce the effect of the treatment. Unfortunately the routine clinical data collected before study enrolment and our general ability to monitor fetal state are not sufficient to allow this hypothesis to be tested. We appreciate S.Bello's comments. The use of a "one in 20 chance" is of course completely arbitrary, although hallowed by common use. The additional analysis reported here might assist in interpreting the clinical significance of the study.	Lancet	2005	365(9471):1620
Rutherford, M., Azzopardi, D., Whitelaw, A., Cowan, F., Renowden, S., Edwards, A.D., Thoresen, M.	*Mild Hypothermia and the Distribution of Cerebral Lesions in Neonates With Hypoxic-Ischemic Encephalopathy*	Hypothermia induced by whole-body cooling (WBC) and selective head cooling (SHC) both reduce brain injury after hypoxia-ischemia in newborn animals, but it is not known how these treatments affect the incidence or pattern of brain injury in human newborns. To assess this, 14 term infants with hypoxic-ischemic encephalopathy (HIE) treated with SHC, 20 infants with HIE treated with WBC, and 52 noncooled infants with HIE of similar severity were studied with magnetic resonance imaging in the neonatal period. Infants fulfilling strict criteria for HIE were recruited into the study after assessment of an amplitude-integrated electroencephalography (aEEG). Cooling was commenced within 6 hours of birth and continued for 48 to 72 hours. Hypothermia was not associated with unexpected or unusual lesions, and the prevalence of intracranial hemorrhage was similar in all 3 groups. Both modes of hypothermia were associated with a decrease in basal ganglia and thalamic lesions, which are predictive of abnormal outcome. This decrease was significant in infants with a moderate aEEG finding but not in those with a severe aEEG finding. A decrease in the incidence of severe cortical lesions was seen in the infants treated with SHC.	Pediatrics	2005	116(4):1001-1006

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Author(s)	Title	Summary	Journal	Year	Vol:Pages
COOL-CAP IN PIGLETS					
Thoresen, M., Simmonds, M., Satas, S., Tooley, J., Silver, I. A.	*Effective Selective Head Cooling During Posthypoxic Hypothermia in Newborn Piglets.*	Selective head cooling has been proposed as a neuroprotective intervention after hypoxia-ischemia in which the brain is cooled without subjecting the rest of the body to significant hypothermia, thus minimizing adverse systemic effects. There are little data showing it is possible to cool the brain more than the body. We have therefore applied selective head cooling to our hypoxia-ischemia piglet model to establish whether it is possible. Nine piglets were anesthetized, and brain temperature was measured at the surface and in the superficial (0.2 cm) and deep (1.7–2.0 cm) gray matter. Rectal (6-cm depth), skin, and scalp temperatures (T) were recorded continuously. Lowering T-rectal from normothermia (39°C) to hypothermia (33.5–33.8°C) using a head cap perfused with cold (6–24°C) water was undertaken for up to 6 h. To assess the impact of the 45-min hypoxia-ischemia insult on the effectiveness of selective head cooling, four piglets were cooled both before and after the insult, and four, only afterward. During selective head cooling, it was possible to achieve a lower T-deep brain than T-rectal in all animals both before and after hypoxia. However, this was only possible when overhead body heating was used. The T-rectal to T-deep brain gradient was significantly smaller after the insult (median, 5.3°C; range, 4.2– 8.5°C *versus* 3.0°C; 1.7-7.4°C; *p* 5 0.008). During rewarming to normothermia, the gradient was maintained at 4.5°C. We report for the first time a study, which by direct measurement of deep intracerebral temperatures, validates the cooling cap as an effective method of selective brain cooling in a newborn animal hypoxia-ischemia model.	Pediatric Research	2001	49(4):594-599
Tooley, J., Satas, S., Eagle, R., Silver, I. A., Thoresen, M.	*Significant Selective Head Cooling Can Be Maintained Long-Term After Global Hypoxia Ischemia in Newborn Piglets*	OBJECTIVE: Selective head cooling (SHC) combined with mild body cooling is currently being evaluated as a potentially therapeutic option in the management of neonatal hypoxic-ischemic encephalopathy. It is proposed that SHC enables local hypothermic neuroprotection while minimizing the deleterious side effects of systemic hypothermia. However, there is little evidence that it is possible to cool the brain more than the body for a prolonged period of time. The aim of this study was to examine whether the brain (T(deep brain)) could be cooled to below the rectal temperature (T(rectal)) in our piglet hypoxia ischemia (HI) model for a period of 24 hours, using a head-cooling cap. METHODS: Eight anesthetized piglets (median age: 15 hours) had subdural and intracerebral basal ganglia temperature probes inserted. After a 45-minute global HI insult (known to produce permanent brain damage), SHC using a cap perfused with cold water (5 degrees C-24 degrees C) combined with overhead body heating to maintain T(rectal) at 34 to 35 degrees C was performed for 24 hours. RESULTS: The piglets were cooled to a median T(rectal) of 35.0 degrees C (interquartile range [IQR]: 34.7-35.3) for 24 hours. During this time, the median T(deep brain) was 31.4 degrees C (IQR: 30 degrees C-32.2 degrees C), with a median T(rectal) to T(deep brain) gradient of 3.4 degrees C (IQR: 2.7 degrees C-4.8 degrees C). At the end of the cooling period, this gradient was still maintained at a median of 3.3 degrees C (IQR: 2.9 degrees C-3.7 degrees C). The ability to obtain the gradient was not influenced by the size of the piglet (1300-1840 g). Cap cooling lowered scalp temperature (T(scalp)) to a median of 24.9 degrees C (IQR: 22.2 degrees C-29.2 degrees C) and subdural temperature to a median of 28.1 degrees C (IQR: 25.8 degrees C-29.5 degrees C) but did not result in either skin injury or superficial brain hemorrhage. There was no clinically useful correlation between T(scalp) and T(deep brain) or between T(scalp) and T(subdural). CONCLUSIONS: This study using our piglet HI model shows that it is possible by means of a head-cooling cap to cool the brain more than the body for a 24-hour period while keeping the core temperature mildly hypothermic. However, we were unable to predict temperatures inside the brain using surface temperature probes on the head	Pediatrics	2002	109(4):643-649

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Author(s)	Title	Summary	Journal	Year	Vol:Pages
		USING COOLING IN PIGLETS			
Iwata, O., Thornton, J.S., Sellwood, M., Iwata, S., Sakata, Y., Noone, M. A., O'Brien, F. E., Bainbridge, A., De Vita, E., Raivich, G., Peebles, D., Scaravilli, F., Cady, E. B., Ordidge, R., Wyatt, J. S., Robertson, N.J.	*Depth of Delayed Cooling Alters Neuroprotection Pattern After Hypoxia-Ischemia*	Hypothermia after perinatal hypoxia-ischemia (HI) is neuroprotective; the precise brain temperature that provides optimal protection is unknown. To assess the pattern of brain injury with 3 different rectal temperatures, we randomized 42 newborn piglets: (Group i) sham-normothermia (38.5-39 degrees C); (Group ii) sham-33 degrees C; (Group iii) HI-normothermia; (Group iv) HI-35 degrees C; and (Group v) HI-33 degrees C. Groups iii through v were subjected to transient HI insult. Groups ii, iv, and v were cooled to their target rectal temperatures between 2 and 26 hours after resuscitation. Experiments were terminated at 48 hours. Compared with normothermia, hypothermia at 35 degrees C led to 25 and 39% increases in neuronal viability in cortical gray matter (GM) and deep GM, respectively (both $p < 0.05$); hypothermia at 33 degrees C resulted in a 55% increase in neuronal viability in cortical GM ($p < 0.01$) but no significant increase in neuronal viability in deep GM. Comparing hypothermia at 35 and 33 degrees C, 35 degrees C resulted in more viable neurons in deep GM, whereas 33 degrees C resulted in more viable neurons in cortical GM (both $p < 0.05$). These results suggest that optimal neuroprotection by delayed hypothermia may occur at different temperatures in the cortical and deep GM. To obtain maximum benefit, you may need to design patient-specific hypothermia protocols by combining systemic and selective cooling.	Annals of Neurology	2005	58(1):75-87
		SELECTIVE HEAD COOLING IN NEONATES			
Battin, M. R., Dezoete, J.A., Gunn, T. R., Gluckman, P., Gunn, A. J.	*Neurodevelop - mental Outcome of Infants Treated With Head Cooling and Mild Hypothermia After Perinatal Asphyxia*	OBJECTIVES: To determine the neurodevelopmental outcome of infants treated with head cooling with systemic hypothermia after hypoxic-ischemic encephalopathy. STUDY DESIGN: Infants >/=37 weeks' gestation, who had an umbilical artery pH </=7.09 or Apgar score </=6 at 5 minutes, plus clinical encephalopathy. Infants with major congenital abnormalities were excluded. TRIAL DESIGN: Infants were allocated to either no cooling (rectal temperature = 37.0 +/- 0.2 degrees C, n = 15), or, sequentially, to head cooling accompanied by different levels of systemic hypothermia, including minimal cooling, rectal temperature 36.5 degrees C to 36 degrees C (n = 6), and mild cooling, to either 35.9 degrees C to 35.5 degrees C (n = 6), 35 +/- 0.5 degrees C (n = 6) or 34.5 +/- 0.5 degrees C (n = 7). Head cooling was accomplished by circulating cooled water through a coil of tubing wrapped around the head for up to 72 hours. Survivors were followed up with regular neurologic examination by a neonatologist until 18 months of age, then with blinded developmental testing using the revised Bayley Scales. RESULTS: A total of 40 term infants were enrolled from 2 to 5 hours after birth. The control and the cooled groups were not significantly different for gestation, birth weight, Apgar score, and initial pH. There were 6 early neonatal deaths (3 normothermic and 3 cooled), and 1 death in infancy associated with severe spastic cerebral palsy in a normothermic infant. Six normothermic, 1 minimally cooled, and 4 mildly cooled infants had early stage 1 encephalopathy; all but 1 had a good outcome. Among infants with early stage 2 or 3 encephalopathy, an adverse outcome was found in 4 of 9 normothermic infants (44%) and 4 of 5 minimally cooled infants (80%), whereas in the combined mildly cooled groups, an adverse outcome was found in 4 of 15 infants (26%, odds ratio 0.46 [0.08, 2.56] vs normothermia). CONCLUSIONS: The present study supports the safety of hypothermia, with no evidence of late adverse effects in any infant. Among infants with moderate to severe encephalopathy at enrollment, there was a tendency toward better outcome. These results emphasize the relatively wide range of outcomes using purely clinical criteria for enrollment. Therapeutic hypothermia should not be used outside of stringent, multicenter trials.	Pediatrics	2001	107(3):480-484

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Author(s)	Title	Summary	Journal	Year	Vol:Pages
Battin, M. R., Penrice, J., Gunn, T.R., Gunn, A. J.	*Treatment of Term Infants With Head Cooling and Mild Systemic Hypothermia (35.0 Degrees C and 34.5 Degrees C) After Perinatal Asphyxia*	OBJECTIVE: To assess the safety of selective head cooling in birth-asphyxiated term newborn infants while maintaining the rectal temperature at 35.0 degrees C or 34.5 degrees C. METHODS: Twenty-six term infants with Apgar <or=6 at 5 minutes or cord/first arterial pH <7.1, plus evidence of encephalopathy, were studied. After parental consent had been obtained, 13 infants received selective head cooling with the rectal temperature maintained at 35.0 degrees C in 6 infants and at 34.5 degrees C in 7 infants. The remaining 13 infants were normothermic. Cooling was achieved by circulating water at 10 degrees C through a cap placed around the head. Rectal, fontanelle, and nasopharyngeal temperatures were monitored. RESULTS: One cooled infant died 2 days after rewarming, and 3 control infants died. Seizures occurred in 9 (69%)of 13 cooled infants and 5 (38%) of 13 control infants. Respiratory support within the first 72 hours of life was required in 10 of 13 infants in both the cooled and control groups. Three cooled infants and 1 control infant received nitric oxide for persistent pulmonary hypertension. During the same interval, 6 of the cooled infants and 4 of the control infants had episodes in which their blood pressure fell to <40 mm Hg; in 2 infants in each group, the lowest blood pressure was below 35 mm Hg. No requirement for volume expansion or increased inotropic support was seen in any infant during stepwise rewarming. All of the cooled infants demonstrated a fall in heart rate during cooling, but the rate was <80/min in only 2 cases and no infant had a rate <70/min. No infant demonstrated an abnormal rhythm or was clinically compromised by the change in heart rate. One infant cooled to a rectal temperature of 34.5 degrees C had a prolonged QT interval of 570 ms associated with a heart rate of 85/min on electrocardiogram aged 34 hours. This returned to normal after rewarming. Platelet counts below 150 x 10(9)/L, hypoglycemia below 2.6 mmol/L, and highest creatinine were not statistically different between cooled and control infants. Positive precooling blood cultures were found in 1 cooled and 1 control infant. The mean cap water input temperature used during cooling was 10 +/- 1 degrees C. During active cooling, the mean difference between rectal and nasopharyngeal temperature was 1.4 degrees C in the infants who were not receiving respiratory support, but this gradient could not be measured in those who were receiving respiratory support that involved delivery of warmed gases to the nasopharynx. CONCLUSIONS: This study suggests that selective head cooling combined with mild systemic hypothermia of 34.4 degrees C or 35.0 degrees C is a stable, well-tolerated method of reducing cerebral temperature in term newborn infants after perinatal asphyxia.	Pediatrics	2003	111(2):244-251

Author(s)	Title	Summary	Journal	Year	Vol:Pages
Gunn, A. J., Gluckman, P., Gunn, T. R.	*Selective Head Cooling in Newborn Infants After Perinatal Asphyxia: a Safety Study*	AIMS: To determine the practicality and safety of head cooling with mild or minimal systemic hypothermia in term neonates with moderate to severe hypoxic-ischemic encephalopathy. METHODS: Study group infants >/=37 weeks' gestation, who had an umbilical artery pH </=7. 09 or Apgars </=6 at 5 minutes, plus evidence of encephalopathy. Infants with major congenital abnormalities were excluded. TRAIL DESIGN: Infants were randomized to either no cooling (controls; rectal temperature = 37.0 +/- 0.2 ° C, n = 10) or sequentially, either minimal systemic cooling (rectal temperature = 36.3 +/- 0.2 ºC, n = 6) or mild systemic cooling (rectal temperature = 35.7 +/- 0.2 ºC, n = 6). Head cooling was accomplished by circulating water at 10 ºC through a coil of tubing wrapped around the head for up to 72 hours. All infants were warmed by servo-controlled overhead heaters to maintain the allocated rectal temperature. The rectal, fontanelle, and nasopharyngeal temperatures were continuously monitored. RESULTS: From January 1996 to October 1997, 22 term infants were randomized from 2 to 5 hours after birth. All infants showed a metabolic acidosis at delivery, with similar umbilical artery pH in the control group (mean +/- standard deviation, 6.79 +/- 0.25), minimal cooling group (6.98 +/- 0.21), and mild cooling group (6.93 +/- 0.11), and depressed Apgar scores at 5 minutes in the control group (4.5 +/- 2), minimal cooling group, (4.7 +/- 2) and mild cooling group (6.0 +/- 1). In the mild-cooled infants, the nasopharyngeal temperature was 34.5 ºC during cooling, 1.2 ºC lower than the rectal temperature. This gradient narrowed to 0.5 ºC after cooling was stopped. No adverse effects because of cooling were observed. No infants developed cardiac arrhythmias, hypotension, or bradycardia during cooling. Thrombocytopenia occurred in 2 out of 10 controls, 2 out of 6 minimal cooling infants, and 1 out of 6 mild cooling infants. Hypoglycemia (glucose <2.6 mM) was seen on at least one occasion in 2 out of 10 controls, 4 out of 6 minimal cooling infants, and 1 out of 6 mild cooling infants. Acute renal failure occurred in all infants. The metabolic acidosis present in all infants at the time of enrollment into the study progressively resolved despite cooling, even in the mild hypothermia group. CONCLUSIONS: Mild selective head cooling combined with mild systemic hypothermia in term newborn infants after perinatal asphyxia is a safe and convenient method of quickly reducing cerebral temperature with an increased gradient between the surface of the scalp and core temperature. The safety of mild hypothermia with selective head cooling is in contrast with the historical evidence of adverse effects with greater depths of whole-body hypothermia. This safety study and the strong experimental evidence for improved cerebral outcome justify a multicenter trial of selective head cooling for neonatal encephalopathy in term infants.	Pediatrics	1998	102(4):885-892
Lin, Z. L., Yu, H. M., Lin, J., Chen, S. Q., Liang, Z. Q., Zhang, Z. Y.	*Mild Hypothermia Via Selective Head Cooling As Neuroprotective Therapy in Term Neonates With Perinatal Asphyxia: an Experience From a Single Neonatal Intensive Care Unit*	Objective: The objective of this study was to determine the efficacy of mild hypothermia via selective head cooling as a neuroprotective therapy in term infants with perinatal asphyxia. Study design: Full-term newborns who had 5 min Apgar scores <6, first arterial blood gas pH<7.10 or BD>15 mEq/l, and with the clinical signs of encephalopathy were enrolled within 6 h after birth. Patients were randomized to receive mild hypothermia treatment via selective head cooling for a total of 72 h or receive routine treatment as a control. Brain hypoxic-ischemic injury was quantified based on the head computed tomographic scan (CT scan) at postnatal age 5-7 days and a Neonatal Behavioral Neurological Assessment (NBNA) score at 7-10 days of life. Results: A total of 58 patients (30 hypothermia, 28 control) completed the study. Hypothermia was well tolerated in this study and attenuated the hypoxic-ischemic brain injury due to perinatal asphyxia. Head CT scan demonstrated moderate to severe hypoxic-ischemic changes in only 4/30 cases from the hypothermic group. In contrast, 18/28 cases in the control group showed moderate to severe hypoxic-ischemic changes (chi (2)=15.97, P<0.01). Brain hypothermia also significantly improved the NBNA score (32+/-2 in the hypothermic group vs 28+/-3 in the control group, P<0.01).Conclusions: Our results suggest that selective head cooling may be used as a neuroprotective therapy in term neonates with perinatal asphyxia. A long-term follow-up study is needed to further validate the results of this study	Journal of Perinatology	2006	26(3):180-184

Author(s)	Title	Summary	Journal	Year	Vol:Pages
Simbruner, G., Haberl, C., Harrison, V., Linley, L., Willeitner, A.E.	*Induced Brain Hypothermia in Asphyxiated Human Newborn Infants: a Retrospective Chart Analysis of Physiological and Adverse Effects*	OBJECTIVE: To assess the physiological effects and adverse side effects of induced hypothermia in asphyxiated newborn infants as a base for future controlled, randomized trials. DESIGN: Retrospective chart analysis with historical controls. SETTING: Tertiary neonatal intensive care unit of the University of Cape Town, South Africa. PATIENTS: Twenty-one asphyxiated newborns treated with induced hypothermia between September 1997 and February 1998 was compared to 15 asphyxiated newborn infants admitted during March to August 1997. The two groups of infants did not differ in patient characteristics or severity of asphyxia (comparison group vs hypothermia group: Apgar at 5 min 5.3 +/- 3.1 vs 5.2 +/- 2.3; base deficit 15.6 +/- 6.3 vs 11.5 +/- 7.2 and Thompson neurological score 10.1 +/- 4.0 vs 9.1 +/- 3.6). INTERVENTIONS: Hypothermia was induced by placing a cap formed from coolpacks, at a temperature of about 10 degrees C, around the head of asphyxiated newborn infants to maintain the nasopharyngeal temperature between 34 and 35 degrees C. Hypothermia was maintained for 3 days. MEASUREMENTS AND RESULTS: In the comparison group 4/15 infants died and in the hypothermia group 4/21 died. Hypothermia was induced at a median of 6.0 h (range 45 min to 53 h) post-partum, maintained for an average of 80 h (median 77.5 h, range 22 to 185 h) and resulted in an average nasopharyngeal temperature of 34.6 +/- 0.5 degrees C. Hypothermia reduced abdominal skin temperature from 36.3 +/- 0.5 degrees C to 35.1 +/- 0.35 degrees C (p = 0.0001), heart rate from 139 +/- 21 to 121 +/- 13 beats/min (p < 0.0001) and respiratory rate from 67 +/- 11 to 56 +/- 9 breaths/min (p = 0.005). Neither episodes of bradycardia nor dysrhythmias, apnea, clinical signs of bleeding diathesis in the hypothermia group nor differences in the frequency of hypoglycaemia and urinary output, blood in urine or tracheal secretion between the two groups were observed. In the survivors the neurological score, assessed at day 2 and day 5, fell from 10.9 +/- 3.5 to 8.1 +/- 4.5 in the hypothermia group and rose from 8.1 +/- 2. 5 to 9.0 +/- 3.1 in the comparison group (p = 0.003). CONCLUSIONS: Adverse effects of mild hypothermia induced for 3 days in asphyxiated newborns were significantly less than expected from previous reports on neonates with accidental hypothermia.	Intensive Care Medicine	1999	25(10):1111 - 1117
Zhou, W. H., Shao, X. M., Cao, Y., Chen, C., Zhang, X. D.	*Safety Study of Hypothermia for Treatment of Hypoxic-Ischemic Brain Damage in Term Neonates*	AIM: To investigate safety an efficacy of mild hypothermia by selective head cooling in term neonates with hypoxic-ischemic brain damage (HIBD). METHODS: Fifty term neonates with Apgar scores $\leq$5 at 5 min, and/or evidence of encephalopathy within 6 h after birth, were randomized to either noncooling, normothermia (NORM, *n*=27), or mild hypothermia group (HYPO, *n*=23), in which head cooling was induced by circulating water for 72 h. Neurodevelopment outcome was assessed at 6 month. RESULTS: The heart rates of the HYPO at 24, 48, and 72 h after treatment dropped to 96$\pm$12, 85$\pm$9, and 96$\pm$16, whereas that of the NORM to 123$\pm$10, 125$\pm$13, and 121$\pm$19, respectively (P<0.05). There was no difference regarding ejection fraction (EF), stroke volume (SV) and cardiac output (CO) between the two groups [(0.61$\pm$0.04) *vs* (0.58$\pm$0.06), (2.3$\pm$0.5) *vs.* (2.4$\pm$0.4) mL/kg, (256$\pm$54) *vs* (277$\pm$42) mL·kg^{-1}·min^{-1}, respectively]. *D*-dimmer and ß2MG were elevated in both groups. The neuron specific enolase (NSE) level of CSF was (26.2$\pm$10.8) mg/L in the HYPO and (34.6$\pm$17.1) mg/L in the NORM (P<0.05). Glutamic acid (GA) was lower in the HYPS [(2.4$\pm$0.8) *vs* (2.9$\pm$1.1) mmol/L, P<0.05]. The neurodevelopment outcome of the patients at 6 mo showed that 18 of 23 patients in the HYPO (78.3%) were considered to have a normal developmental quotient (DQ) compared with 19 of 27 (70.4%) in the NORM. CONCLUSION: The results of our pilot study suggest that mild hypothermia does not aggravate cardiac, kidney and coagulation function, but has a potential of neuroprotection, It warrants a randomized controlled clinical study to verify its efficacy in HIBD.	Acta Pharma-cologica Sinica	2002	23:64-68

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Author(s)	Title	Summary	Journal	Year	Vol:Pages
RECENT REVIEWS – HYPOTHERMIC TREATMENT OF HIE NEONATES					
Gunn, A. J., Battin, M., Gluckman, P., Gunn, T. R., Bennet, L.	*Therapeutic Hypothermia: From Lab to NICU*	The possibility of a therapeutic role for cerebral hypothermia during or after resuscitation from perinatal asphyxia has been a long-standing focus of research. However, early studies had limited and contradictory results. It is now known that severe hypoxia-ischemia may not cause immediate cell death, but may precipitate a complex biochemical cascade leading to the delayed development of neuronal loss. These phases include a latent phase after reperfusion, with initial recovery of cerebral energy metabolism but EEG suppression, followed by a secondary phase characterized by accumulation of cytotoxins, seizures, cytotoxic edema, and failure of cerebral oxidative metabolism from 6 to 15 h post insult. Although many of the secondary processes can be injurious, they appear to be primarily epiphenomena of the 'execution' phase of cell death. This conceptual framework allows a better understanding of the experimental parameters that determine effective hypothermic neuroprotection, including the timing of initiation of cooling, its duration and the depth of cooling attained. Moderate cerebral hypothermia initiated in the latent phase, between one and as late as 6 h after reperfusion, and continued for a sufficient duration in relation to the severity of the cerebral injury, has been consistently associated with potent, long-lasting neuroprotection in both adult and perinatal species. The results of the first large multicentre randomized trial of head cooling for neonatal encephalopathy and previous phase I and II studies now strongly suggest that prolonged cerebral hypothermia is both generally safe - at least in an intensive care setting - and can improve intact survival up to 18 months of age. Both long-term follow-up studies and further large studies of whole body cooling are in progress.	Journal of Perinatal Medicine	2005	33(4):340-346
Thoresen, M., Whitelaw, A.	*Therapeutic Hypothermia for Hypoxic-Ischaemic Encephalopathy in the Newborn Infant*	PURPOSE OF REVIEW: This review examines recent findings from experimental models and clinical trials of induced hypothermia as treatment after cerebral hypoxia-ischaemia in term newborn infants. RECENT FINDINGS: Experimental hypothermia inhibits many steps in the biochemical cascade that produces severe brain injury after hypoxia-ischaemia. This is in contrast to pharmacological agents, which tend to target only one step in the process that leads to brain injury. In adult humans hypothermia initiated immediately after cardiac arrest has improved outcomes. Delayed cooling after brain trauma has also been effective in a subgroup of adult patients. Seventy-two hours of selective head cooling with mild systemic hypothermia (rectal temperature 34.5 degrees C) in term infants with hypoxic-ischaemic encephalopathy (HIE) reduced death or disability in the infants with less severe electroencephalographic changes at entry (no benefit in those with advanced electroencephalographic changes). Cooling had no apparent adverse effects. A smaller randomized clinical trial of 48 h whole body cooling (rectal T 33 degrees C) found a reduction in death and neurological impairment. SUMMARY: In term infants with HIE there is emerging evidence that both selective head cooling and whole body cooling are neuroprotective and safe. This is consistent with a wealth of experimental animal data and adult trials. Neuroprotection seems to be lost if cooling is started after 6 h. The challenge now is to complete ongoing trials. If meta-analysis confirms a therapeutic effect, then this may lead to selection criteria and treatment protocols for very early hypothermia in HIE at term.	Current Opinion in Neurology	2005	18(2):111-116
HISTORICAL REVIEW – HYPOTHERMIC TREATMENT OF HIE NEONATES					
Thoresen, M., Wyatt, J.	*Keeping a Cool Head, Post-Hypoxic Hypothermia - An Old Idea Revisited*	Hypoxia-ischaemia produces permanent brain damage by processes that continue for many hours after reoxygenation/reperfusion. This provides a window of opportunity for therapy aimed at preventing further loss of brain cells. Reducing brain temperature by 2-6 degrees C for 3-72 h after reoxygenation/reperfusion has been shown to reduce brain damage by 25-80% in controlled trials with six different neonatal animal models of hypoxia-ischaemia. No adverse effects from mild hypothermia have been documented. The mechanisms of protection are unknown but may include a reduction in extracellular excitotoxic amino acids, reduced nitric oxide synthesis and inhibition of apoptosis. Mild hypothermia is currently the most promising clinically feasible neural rescue therapy for full-term infants at risk of developing hypoxic-ischaemic encephalopathy, but clinical use must be restricted to approved trial protocols.	Acta Paediatr	1997	86(10):1029 - 1033

Author(s)	Title	Summary	Journal	Year	Vol:Pages
		NEW ARTICLES			
Gunn, A. J., Thorese, M.	*Hypothermic neuroprotection*	The possibility that hypothermia during or after resuscitation from asphyxia at birth, or cardiac arrest in adults, might reduce evolving damage has tantalized clinicians for a very long time. It is now known that severe hypoxia-ischemia may not necessarily cause immediate cell death, but can precipitate a complex biochemical cascade leading to the delayed neuronal loss. Clinically and experimentally, the key phases of injury include a latent phase after reperfusion, with initial recovery of cerebral energy metabolism but EEG suppression, followed by a secondary phase characterized by accumulation of cytotoxins, seizures, cytotoxic edema, and failure of cerebral oxidative metabolism starting 6 to 15 h post insult. Although many of the secondary processes can be injurious, they appear to be primarily epiphenomena of the 'execution' phase of cell death. Studies designed around this conceptual framework have shown that moderate cerebral hypothermia initiated as early as possible before the onset of secondary deterioration, and continued for a sufficient duration in relation to the severity of the cerebral injury, has been associated with potent, long-lasting neuroprotection in both adult and perinatal species. Two large controlled trials, one of head cooling with mild hypothermia, and one of moderate whole body cooling have demonstrated that post resuscitation cooling is generally safe in intensive care, and reduces death or disability at 18 months of age after neonatal encephalopathy. These studies, however, show that only a subset of babies seemed to benefit. The challenge for the future is to find ways of improving the effectiveness of treatment.	NeuroRx	2006	3(2):154-169
Edwards, A., Azzopardi, D.	*Therapeutic hypothermia following perinatal asphyxia*	Well-constructed and carefully analyzed trials of hypothermic neural rescue therapy for infants with neonatal encephalopathy have recently been reported. The data suggest that either selective head cooling or total body cooling reduces the combined chance of death or disability after birth asphyxia. However, as there are still unanswered questions about these treatments, many may still feel that further data are needed before health care policy can be changed to make cooling the standard of care for all babies with suspected birth asphyxia.	Arch Dis Child Fetal Neonatal Ed	2006	91(2):127-131