

CoolCap Clinical Trial

Selective head cooling demonstrated to be safe and effective in preventing or reducing severity of neurologic injury associated with HIE

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Overview

A clinical trial sponsored by Olympic Medical has shown selective head cooling to be safe and effective for treatment of neonatal hypoxic-ischemic encephalopathy (HIE).

Trial Description

The CoolCap clinical trial was an international multicenter, prospective randomized control study. Enrollment occurred July 1999 through January 2002, and follow-up was completed in September 2003.

Within six hours of birth, after inclusion/exclusion criteria were met and informed consent was obtained, infants were randomized to either a non-cooled (normothermia) control group with rectal temperature maintained at $37.0 \pm 0.5^{\circ}\text{C}$, or to a treatment group for head cooling with mild systemic hypothermia with rectal temperature maintained at $34.0 \pm 0.5^{\circ}\text{C}$ for 72 hours.

Infant Assessment

Prior to treatment, and as a component of the inclusion criteria, aEEG/CFM recordings were taken and analyzed by qualified personnel. During the 72-hour treatment, cardiovascular, hematologic, metabolic, blood chemistry, and temperature data were recorded.

At 18 months, infants completed the study with the following: neurodevelopmental examination; measurements of weight, length, and head circumference; psychometric testing with Bayley-II; audiology assessment; and ophthalmology examination. All exams were performed by qualified personnel who were blinded to the treatment.

Primary outcome in the CoolCap clinical trial was the combined rate of mortality and severe neurodevelopmental disability in survivors at 18 months of age. Severe neurodevelopmental disability constituted the presence of any one of the following: (a) Gross Motor Function (GMF) impairment level 3-5, (b) Bayley mental scale (MDI) < 70 , or (c) bilateral cortical visual impairment.

Study Population

A total of 25 sites enrolled 234 infants in the clinical trial. Of these 234 infants, 75% (176/234) were enrolled at sites in the United States and 25% (58/234) were enrolled internationally. The international enrollees were distributed as follows: 11% (26/234) in England, 9% (21/234) in Canada, and 5% (11/234) in New Zealand.

Baseline infant characteristics were generally well balanced with the exception of Apgar score at five minutes after birth and aEEG/CFM background (both had more severely affected infants in the cooled group).

Safety

There was no statistically significant difference in the occurrence of serious adverse events between the two groups. Two anticipated adverse events occurred more frequently in the cooled group: minor cardiac arrhythmias and head/scalp edema.

Minor cardiac arrhythmias occurred in 10 (9%) of cooled infants as compared to 1 (1%) control infant. Although there was a higher incidence of minor cardiac arrhythmias in the cooled infants, this was expected since mild sinus bradycardia is known to be associated with hypothermia. Note, however, that none of the cooled infants experienced a major cardiac arrhythmia.

Scalp edema occurred in 21% (23/112) of the cooled infants. All except three of the edema cases were of mild to moderate severity. Furthermore, all 23 cases of scalp edema resolved prior to or after completion of cooling treatment with either no action or massage, changing position, or cap adjustment.

There was also a statistically significant ($p=0.02$) decrease in the incidence of elevated liver enzymes: 38% (42/112) in the cooled infants as compared to 53% (62/118) in the control infants.

Effectiveness

As shown in Chart 1, complete 18-month primary outcome results were available in 93% (218/234) of the infants. Of the 218 infants, 50% (110/218) were in the control group and 50% (108/218) in the cooled group. The control group had a favorable outcome of 34% (37/110), while the cooled group had a favorable outcome of 45% (49/108). Fisher's exact test showed no statistical significance ($p=0.10$; 11% difference, 95% confidence interval -1% to 25%).

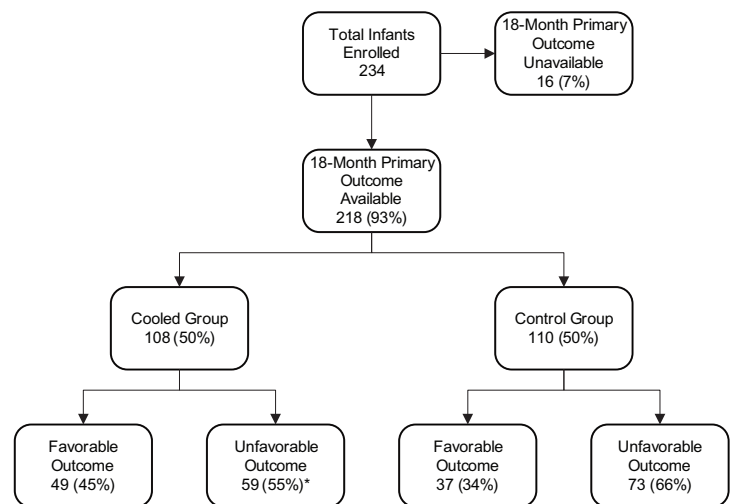
However, the randomization resulted in a greater proportion of infants with severe aEEG baseline in the cooled group (37% or 40/108) as compared to the control group (28% or 31/110). A six-factor logistic regression analysis adjusting for baseline aEEG background, aEEG seizure status, Apgar score, birth weight, gender, and age at randomization indicated a treatment effect of statistical significance ($p=0.042$; odds ratio 0.53, 95% confidence interval 0.29-0.98) with a number-needed-to-treat (NNT) of 6.

Furthermore, four of the infants who were randomized to cooling did not receive treatment. Since all four of these infants had an unfavorable outcome, the incidence of favorable outcome in treated infants was 49% (49/104) resulting in a difference in incidence of 15% (49% vs. 34%). A "per treatment" analysis excluding these four infants ($n=214$) yielded a statistically signif-

icant finding even for the Fisher's exact test ($p=0.04$) and a finding of increased statistical significance for the six-factor logistic regression analysis ($p=0.02$).

Therefore, it may be concluded that, in full-term neonates with moderate to severe hypoxic-ischemic encephalopathy, selective head cooling with mild systemic hypothermia, when administered with the Olympic Cool-Cap® in the manner described, is associated with a reduction in the combined endpoint of death and severe neurodevelopmental disability.

Chart 1:
Primary outcome for the CoolCap trial



*includes four infants who did not receive treatment

Mortality and Withdrawal of Care

With regard to mortality, as shown in Table 1, there was no statistically significant difference in the death rates for the two study groups ($p=0.48$) although there was a trend toward decreased mortality in the cooled group. Specifically, mortality rates were 31% (36/116) in the cooled group and 36% (42/118) in the control group.

Furthermore, 12 of the 27 deaths during the first eight days in the cooled group occurred after treatment was completed. This demonstrates that care can still be withdrawn from infants with profound HIE even if withdrawal is delayed until after hypothermia treatment.

Table 1: Mortality rates for enrolled population (n=234)

Survival Status	Cooled (n=116)	Control (n=118)	Total (n=234)
Alive	73 (63%)	71 (60%)	144 (62%)
Dead	36 (31%)	42 (36%)	78 (33%)
Unknown	7 (6%)	5 (4%)	12 (5%)

No Death-to-Disability Shift

Finally, as shown in Table 2, a review of the data further shows that there is no evidence of a shift from death to disability for the cooled infants. There is no increase in the forms of disability measured as primary outcome. In fact, there is a trend toward decreased incidence in all forms of disability.

Table 2: 18-month primary outcome components for survivors

Primary Outcome Components	Cooled	Control	Total	Fisher's Exact p-Value
Neuromotor Disability per GMF \geq 3				
No	58 (81%)	47 (69%)	105 (75%)	
Yes	14 (19%)	21 (31%)	35 (25%)	0.12
Bayley MDI				
\geq 70	49 (70%)	37 (61%)	86 (66%)	
< 70	21 (30%)	24 (39%)	45 (34%)	0.27
Bilateral Cortical Visual Impairment				
No	65 (90%)	53 (83%)	118 (87%)	
Yes	7 (10%)	11 (17%)	18 (13%)	0.22

Conclusions

The Olympic Cool-Cap[®] was successfully tested in an international randomized control trial for 234 infants. Treatment was started within six hours of birth and a rectal temperature of $34.0 \pm 0.5^{\circ}\text{C}$ was maintained for 72 hours.

With regards to safety, minor cardiac arrhythmias occurred in 10% of treated infants and scalp edema occurred in 21% of treated infants. Mild sinus bradycardia is associated with hypothermia and resolves upon rewarming. Scalp edema resolves either during or after completion of treatment and has no long-term sequelae.

Nearly half of the cooled infants (45% for 'per protocol' and 49% for 'per treatment') experienced a favorable outcome. This compared with a 34% incidence of favorable outcome in the control infants. This was a statistically significant finding and yielded a number-needed-to-treat of 6.

Trial data confirmed that life support can still be withdrawn from infants with profound HIE even if delayed until after hypothermia treatment. Furthermore, there is no evidence that treatment moves infants from death to a lifetime of disability.

Thus it may be concluded that the Olympic Cool-Cap[®] safely and effectively provides selective head cooling with mild systemic hypothermia to prevent or reduce the severity of neurologic injury associated with HIE.



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