

## **Dysphagia in Encephalopathic Neonates Treated with Hypothermia**

A thesis submitted to the University of Arizona College of Medicine -- Phoenix  
in partial fulfillment of the requirements for the degree of Doctor of Medicine

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Class of 2013

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**Acknowledgements:**

The authors would like to thank Cristina Carballo, MD; Kim Allred, NNP; and Pamela Clarke-Levens, NP of the Department of Neonatology - Phoenix Children's Hospital for their invaluable input regarding the clinical details of this study. We would also like to thank Igor Dvorchik, PhD of the Children's Neuroscience Institute - Phoenix Children's Hospital for his assistance with statistical analysis. Richard Towbin, MD and John Curran, MD of the Department of Radiology - Phoenix Children's Hospital are also deserving of acknowledgement for lending us their guidance and expertise.

**Abstract:**

**Objective:** The purpose of this study is to determine the rate of dysphagia in neonates treated with targeted body temperature reduction as compared to neonates who have not been exposed to hypothermia.

**Methods:** We performed a retrospective study of encephalopathic neonates who were treated with hypothermia and who underwent a modified barium swallow (MBS). For comparison, a group of neonates who had been evaluated with MBS but did not receive hypothermic therapy was identified. This group consisted of non-encephalopathic patients. MBS results were qualified as either normal or abnormal.

**Results:** There was no statistically significant difference in the percentage of abnormal MBS results between the hypothermic and control groups (Fisher's exact;  $P = 0.78$ ). The odds ratio for abnormal MBS results in the hypothermia group relative to the control group was 1.2, with 95% confidence interval of 0.42 to 3.8.

**Significance:** These data indicate that hypothermia does not seem to increase short term risk of dysphagia compared to the control group. There is no apparent association between hypothermia and dysphagia. This supports previous findings that hypothermia is a safe treatment for neural injuries in NICU patients.

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## **Introduction:**

### Background:

Multiple studies have reported improved primary outcomes for encephalopathic neonates treated with targeted temperature reduction (hypothermia).<sup>1-7</sup> In addition, the safety of hypothermia has been validated without reported increase in adverse effects. Despite its reported effectiveness, a large percentage of treated neonates still do not demonstrate favorable outcomes. The rate of death or severe disability assessed at 18 to 21 months of age in treated neonates still ranges from 44-55% according to the larger hypothermia trials (TOBY<sup>1</sup>, NICHD<sup>5</sup>, Cool Cap<sup>6</sup>, neo.nEURO.network<sup>8</sup>).

In an attempt to improve on these outcomes, there is a concerted effort to study and maximize the efficacy of hypothermia treatment. Much of this focus centers on the treatment phase; investigating factors such as the timing of initiation, duration of cooling, inclusion criteria, and the specifics of temperature modification itself.<sup>9-12</sup> There is currently less discussion and literature regarding the effects of hypothermic therapy on possible adverse effects during the treatment phase. This may be due to reports from the prior large, randomized studies demonstrating the efficacy and safety of hypothermia. These studies found that hypothermia had no significant effect on a number of potential complications commonly associated with neonatal encephalopathy. Adverse effects such as bradycardia, coagulopathy, pulmonary hypertension and seizure in treated groups were compared to controls without a statistically significant increase in incidence.<sup>13-16</sup> To our knowledge, the assessment of swallowing function has not been previously reported in any organized study of neonatal hypothermic therapy.

At our institution, neonates diagnosed with encephalopathy are routinely treated with targeted body temperature reduction through the use of either whole body cooling or direct cooling of the head utilizing a specialized "Cool Cap." When dysphagia is clinically suspected in neonates at our institution, swallowing function is evaluated with a modified barium swallow (MBS). This

videofluoroscopic test provides dynamic images of the oral, pharyngeal and esophageal phases of swallowing. This exam is performed jointly by a speech pathologist and radiologist and is useful for assessing the integrity of the swallowing reflex and for determining the consistencies of formula least likely to result in aspiration.

Impact:

Dysphagia is a prevalent and persistent problem for children who survive early, severe neurological injury. A number of prior studies have reported a range of values for the incidence of swallowing dysfunction in varied cohorts of children with cerebral palsy.<sup>17-22</sup> The majority of these recently published studies utilized noninvasive, clinical methods such as observation of mealtime feeding, parental interviews and review of medical records. Regardless of the methodology, a consistently high incidence of dysphagia was observed which ranged from 58-99%. Unfortunately, neonates are an under-represented cohort in these studies. Given the potential sequelae of swallowing dysfunction and aspiration, it is very plausible that clinically occult dysphagia could significantly impact the morbidity and mortality of this already fragile patient population.

Aims:

Previously, clinicians at our institution and their colleagues noted a seemingly increased rate of abnormal MBS results in hypothermically treated neonates. This study was conceived to determine the rate of dysphagia in encephalopathic neonates treated with therapeutic hypothermia. Due to the fact that hypothermia has become the standard of care for neonatal encephalopathy, a contemporary control group of normothermic, encephalopathic neonates could not be identified. Thus, in order to delineate a baseline level of comparison for the study group, the incidence of swallowing dysfunction identified by MBS was also calculated for a historical population of normothermic, non-encephalopathic neonates. Based upon our previous experience with this population, we hypothesize that the hypothermic group of

patients will exhibit a significantly higher incidence of dysphagia than the normothermic group. To our knowledge, this is the first study to address a possible association of hypothermia with swallowing dysfunction.



## Research Materials and Methods:

This study was approved by our institutional review board.

### Hypothermia Group Inclusion Criteria:

We retrospectively identified neonatal intensive care unit (NICU) patients at our institution from January 2009 to December 2010 who underwent hypothermia for treatment of encephalopathy and who received at least one MBS study within the neonatal period.

### Hypothermia Selection Criteria:

All three of the following criteria were required for initiation of hypothermia:

1. The patient must have been born at 36 weeks of gestation or greater.
2. The patient must have exhibited at least one of the following:
  - a. Apgar score less than or equal to five at 10 minutes.
  - b. Continued need for resuscitation (intubation or mask ventilation) at 10 minutes.
  - c. Umbilical cord or arterial pH of less than 7.00 within 60 minutes of birth.
  - d. Base deficit of  $-16$  mmol/L in any blood sample within 60 minutes of birth.
3. The patient must have displayed altered consciousness as evidenced by lethargy, stupor or coma *plus* at least one of the following:
  - a. Hypotonia.
  - b. Abnormal reflexes (including oculomotor and/or pupillary).
  - c. Absent or weak suck.
  - d. Clinical seizures.

Qualification for the Cool Cap also required a 20 minute amplitude-integrated electroencephalogram (aEEG) recording that displayed abnormal background activity or seizure. Criteria for the cooling blanket did not require aEEG. Neonates greater than six hours of age before therapy could be initiated were not cooled. Patients with imperforate anus (due

to prevention of rectal temperature readings), evidence of head trauma or skull fracture, or birth weight less than 1800 grams did not qualify for hypothermic therapy.

#### Hypothermia Protocol:

The hypothermia protocol was initiated within six hours of injury and consisted of either a Cool Cap (selective head cooling) or cooling blanket (whole body cooling). Target body temperature for the cooling blanket was 33.5 degrees Celsius. Target body temperature for the Cool Cap was 34.5 degrees Celsius. Hypothermia was maintained for 72 hours at which point patients were re-warmed at a rate of 0.5 degrees Celsius per hour.

#### Control Group:

We retrospectively identified NICU patients at our institution from January 2009 to December 2010 who did not receive hypothermic therapy, but who did undergo at least one MBS study within the neonatal period. These patients were non-encephalopathic.

#### Exclusion Criteria:

Patients with a birth weight less than 1800 grams or gestational age less than 36 weeks were excluded from this study. In addition, patients with a diagnosis that would likely confound MBS results such as: tracheo-esophageal fistula (TEF), esophageal atresia, Down syndrome, and/or micrognathia were excluded.

#### MBS:

Initially in the NICU, patients had the opportunity to practice oral feeds of 15cc volume every three hours for several days. If these feeds were tolerated without difficulty, the patient was evaluated with MBS performed by offering the patients barium liquid of various consistencies. Fluoroscopy was utilized to visualize the phases of swallowing. MBS results for each neonate were classified as normal or abnormal. Normal MBS results were defined as normal swallowing, nasopharyngeal reflux, or laryngeal penetration. Aspiration in any of the tested consistencies was considered abnormal.<sup>23</sup>

#### Statistical Methods:

A biostatistician assisted the authors with selection of statistical methods and the required calculations. The demographic data of the two groups (gestational age, birth weights, age at MBS) were compared with simple calculation of the mean and standard deviation. The incidences of abnormal MBS results between the two groups were compared using Fischer's exact test ( $\alpha = 0.05$ ). The odds ratio and 95% confidence intervals have also been provided.

## Results:

Thirty-three neonates were identified in the hypothermia group. The control group consisted of thirty-five neonates. The hypothermia and control groups had similar mean gestational ages [mean +/- standard deviation (SD): hypothermia 39.1 +/- 1.6 weeks; control 38.7 +/- 1.5 weeks] and similar mean birth weights (mean +/- SD: hypothermia 3470 +/- 545 grams; control 3183 +/- 366 grams). Likewise, the two groups underwent MBS at similar ages (mean +/- SD: hypothermia 11.2 +/- 5.6 days; control 15.3 +/- 6.6 days).

MBS results for the two groups are presented in Table 1. There was no statistically significant difference in the percentage of abnormal MBS results between the hypothermic and control groups (Fisher's exact;  $P = 0.78$ ). The odds ratio for abnormal MBS results in the hypothermia group relative to the control group was 1.2, with 95% confidence interval of 0.42 to 3.8.

**Table 1.**

	Hypothermia (N = 33)	Control (N = 35)
Normal MBS	24 (73)	27 (77)
Abnormal MBS	9 (27)	8 (23)

Data given as n (%)

**Discussion:**

Currently there is fairly homogeneous, evidence-based support for hypothermia in the treatment of neonatal encephalopathy. Given the results of the larger randomized trials (TOBY<sup>1</sup>, NICHD<sup>5</sup>, Cool Cap<sup>6</sup>, neo.nEURO.network<sup>8</sup>) and the subsequent meta-analysis by Edwards *et al.*<sup>4</sup>, most clinicians at specialized centers with the appropriate resources advocate the initiation of hypothermic therapy for encephalopathic neonates meeting the entrance criteria. Hypothermia has been demonstrated to improve the primary outcome of these studies: reducing the rate of death or severe disability assessed at 18 to 21 months of age. However, there is still significant room for improvement. Several current lines of study are attempting to improve on these outcomes by addressing factors related to the application of the hypothermia treatment. This treatment focused research includes trials assessing which neonates are the most likely to benefit from treatment, the efficacy of treatment en route to specialized centers, and studies related to the window for treatment initiation, duration and the specifics of rewarming.<sup>9-12</sup> By contrast, relatively few research efforts are currently being devoted to the possibility of adverse effects related to targeted body temperature reduction.

The focus of this study is to determine the prevalence of swallowing dysfunction during the diagnosis and hypothermic treatment of encephalopathic neonates. Dysphagia is reported to be a very prevalent complication in children who have suffered severe neurological injury.<sup>13</sup> However, little has been reported on the diagnosis of dysphagia by radiological assessment in the neonatal population and no prior studies involving neonates treated with hypothermia exist. Currently, the effectiveness of hypothermic therapy is measured by assessment of childhood mortality and morbidity at 18-21 months. Any increased prevalence of dysphagia in this population could lead to respiratory complications that affect morbidity and mortality, thus affecting the interpretation of treatment efficacy.

In this study, when comparing the prevalence of dysphagia in a hypothermic study group relative to a control group, we find no statistically significant difference between the two. This supports the supposition that hypothermia is a safe therapy with relatively few adverse effects.

Indeed; bradycardia, coagulopathy, pulmonary hypertension, and seizure have all been similarly addressed in previous studies and no statistically significant difference was found between treatment and control groups.<sup>14-17</sup>

An interesting incidental finding of this study was the high percentage of abnormal MBS results (23%) in the control group of neonates who were not exposed to hypothermia. While the incidence of swallowing dysfunction in hypothermic neonates has not been previously reported, the incidence of dysphagia in normothermic pediatric patients has been previously investigated. Mercado-Deane *et al.* previously discovered a sizable prevalence of swallowing dysfunction (13.4%) as measured by upper gastrointestinal (UGI) study in patients less than one year of age who had no history of prematurity, cardiac disease, neurological disease, or other chronic illness.<sup>25</sup> MBS was utilized in the aforementioned study, but only to confirm abnormal UGI results. Lefton-Greif *et al.* also noted a high incidence of aspiration (57.9%) amongst a group of 19 patients with an average age of 1.14 years who presented with unexplained respiratory symptoms and subsequently underwent MBS.<sup>27</sup> The wide gap in the average ages between Lefton-Greif *et al.* and this study makes comparisons between our findings difficult. Finally, Vasquez *et al.* performed a study of MBS in 17 neonates and found a prevalence of 76% abnormal results.<sup>27</sup> Unlike our study, Vasquez *et al.* included premature infants and infants with congenital malformations such as TEF. Such patients were excluded in our study which likely accounts for the higher estimate of the incidence by Vasquez *et al.* Overall, the previously reported prevalences of dysphagia in infants range from 13.4% to 76%. Our estimate (23%) sits on the lower end of this range, but is nevertheless higher than what might be expected by clinicians who care for NICU patients routinely.

It is important to note that in light of their NICU admission, the groups in this study are unlikely to approximate the general (non-hospitalized) neonatal population. Our findings should therefore not be generalized to normal, healthy neonates. The similar clinical status of the two groups however, does make them ideal for comparison to each other.

## **Future Directions:**

This study found no statistically significant difference in the percentage of patients exhibiting abnormal MBS results in hypothermic versus normothermic groups of neonates. This supports the assertion that hypothermia is a safe therapy for the treatment of neurological injuries in neonates. Ongoing studies continue to refine hypothermia protocols in order to maximize favorable outcomes. However, clinicians caring for this patient population should remain vigilant for any adverse effects of such therapy in order that they can be further investigated.

This study also notes an unexpectedly high percentage of NICU patients displaying aspiration on MBS in both the hypothermic and normothermic groups. The high incidence of dysphagia in the normothermic NICU population is surprising and may warrant further study with more in depth examination of patient co-morbidities.

Given that this patient population has suffered neurological injury, which is often characterized and diagnosed by neurological imaging (such as MRI of the brain), it would be interesting to examine if there is any correlation between the characteristics of the neuroimaging findings and the severity of dysphagia in these patients.

Aspiration is likely a risk factor for respiratory disease in this fragile patient population. It would be interesting to follow patients over the course of their illness and note whether or not those patients with MBS demonstrative of aspiration developed respiratory complications with higher frequency than those who did not; and if so, did those patients suffer higher morbidity and mortality?



**Conclusions:**

In this study, we report no statistically significant difference in swallowing dysfunction between neonates treated with hypothermia and normothermic neonates. This supports the supposition that hypothermia is a safe therapy for treatment of neural injury in neonates. However, in light of the surprisingly high percentage of abnormal MBS results in both the hypothermic and normothermic groups of patients, it may be prudent to increase surveillance for swallowing abnormalities amongst neonates admitted to the NICU. Clinicians should maintain a high level of suspicion for dysphagia and aspiration in the critically ill neonatal population.

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