Therapeutic Hypothermia Following Perinatal Asphyxia

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Summary and Conclusions

SBU's appraisal of the evidence

During birth, asphyxia occurs when the child suffers a combination of oxygen deficiency and reduced blood supply. In serious cases of asphyxia, the infant can develop symptoms of brain damage shortly following birth, ie, hypoxic ischemic encephalopathy (HIE). In moderate to severe asphyxia the lack of oxygen can cause serious damage to the brain and other organs, and some of the infants die. Children who survive are at higher risk for moderate or severe functional impairments, eg, cerebral palsy (CP) or impaired vision and hearing. Therapeutic hypothermia is a new method for treating HIE following birth asphyxia and is used to complement standard treatment.

- In full-term newborns affected by moderate or severe symptoms of brain injury (HIE) due to severe birth asphyxia, therapeutic hypothermia reduces the risk of death or severe functional impairment in the child (Evidence Grade 2)*. However, the scientific evidence is insufficient* to appraise the method's effect beyond 18 months.

- The scientific evidence is insufficient* to draw firm conclusions on the adverse effects and complications related to therapeutic hypothermia. No serious adverse effects or complications have been identified in the studies reviewed for this report, but the studies were not specifically designed to investigate this.

- The scientific evidence is insufficient* to draw firm conclusions on the cost-effectiveness of the method. However, the fact that the extra costs for this method are relatively moderate and the outcomes are good would suggest that the method is cost-effective.

- The optimum way (best practice) to deliver treatment is not clear. Hence, it is important to monitor the experiences and outcomes of treatment, eg, via a central quality register. Also, continued research is essential to gain knowledge about best practices as well as the potential complications and adverse effects.

* Criteria for Evidence Grading SBU's Conclusions, see page 2.

TARGET GROUP AND TECHNOLOGY The potential target group for therapeutic hypothermia includes full-term infants who have been affected by moderate or severe symptoms of HIE following serious asphyxia in conjunction with birth. In Sweden, 50 to 200 children per year could be potential candidates for therapeutic hypothermia.

Therapeutic hypothermia involves lowering the child's body temperature to 33–35 degrees for 72 hours, which can be done by cooling the head only, or the whole body. Afterwards, the child's body temperature is slowly raised to normal. Treatment requires specially trained staff and special cooling and monitoring devices. In Sweden, therapeutic hypothermia is not an established treatment method for HIE following birth asphyxia in newborns. The method is used, however, in approximately 10 hospitals across Sweden, mostly university hospitals.

Standard treatment for children with HIE is supportive and symptom relieving. Treatment includes neonatal intensive care since several organ systems can fail. During the past decade, clinical studies have shown that therapeutic hypothermia introduced within 6 hours of birth can have a protective effect on the brain.

PRIMARY QUESTIONS

- What effects does therapeutic hypothermia have on mortality and survival with moderate or severe functional disabilities in full-term infants affected by moderate or severe symptoms of hypoxic ischemic encephalopathy (HIE) following serious birth asphyxia?
- What are the potential complications and adverse effects of treatment?
- What does the treatment cost? Is it cost-effective?

PATIENT BENEFIT Three systematic reviews, appraised to be of high quality, show that therapeutic hypothermia of full-term infants with moderate or severe HIE following severe birth asphyxia reduces the risk of death or survival with severe functional disabilities. The children were followed until they were at least 12

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months of age, but no older than 18 months. The results are statistically significant and clinically meaningful. The relative risk reduction was 22% to 24%, and the absolute risk reduction was 14 to 16 percentage points. This means that of 100 children with HIE who receive therapeutic hypothermia, on average 14 to 16 more children will survive without severe functional disabilities compared to if they hadn't received therapeutic hypothermia. In separate analyses of the two endpoints, ie, death and survival with moderate/severe functional disabilities, the reviews show that therapeutic hypothermia reduces risk for both outcomes.

No serious adverse effects or complications related to therapeutic hypothermia have been identified in the studies reviewed in this report, but there are no well-executed studies that have been specifically designed to investigate this.

ETHICAL ASPECTS The quality of life for children receiving therapeutic hypothermia increases since fewer children die and fewer have severe functional disabilities. Likewise, the quality of life for parents and siblings also increases. This, however, must be weighed against the uncertainty regarding the optimum way to deliver the treatment and its long-term effects.

Therapeutic hypothermia must begin within 6 hours of birth. Access to therapeutic hypothermia varies in different parts of Sweden. Hence, there is a risk that therapeutic hypothermia cannot be offered within 6 hours to all children needing this care, which conflicts with the so-called equity principle in Sweden. Given the current diffusion of this method, hospitals need to have a high level of collaboration and a well functioning transportation system.

Starting therapeutic hypothermia requires an immediate decision. Hence, healthcare staff do not always have time to confer with the child's parents before starting treatment. As quickly as possible, the parents should receive comprehensive, objective, and well-designed information about the method's potential benefits and risks.

When the method is introduced in clinical practice there is a risk that the inclusion criteria used in the research studies, and which are currently recommended for clinical use, will not be strictly applied. This could result in treating children who are too severely damaged to benefit from therapeutic hypothermia, leading to survival with very severe functional disabilities that affect quality of life not only for the child, but also for the family. Less stringent application could also lead to unnecessarily treating children who do not have sufficiently severe injuries, and hence do not meet the criteria for therapeutic hypothermia. Against this background, it is important to follow the children who are treated and to coordinate this data in a quality register. Assuming that all children who require therapeutic hypothermia can receive it, that the parents' informational needs are met, and that the children are carefully followed up, the method is appraised to be ethically defensible given its benefits regarding quality of life.

ECONOMIC ASPECTS The average extra cost per child receiving therapeutic hypothermia is roughly estimated at 5000 to 10 000 Swedish kronor (SEK), including the extra staff costs during the care episode. Additional costs would include any costs for transportation to and from the home hospital and the cost for followup examinations of the child's motor and cognitive development. The only health economic study available, an American model study, shows that therapeutic hypothermia offers better effects at a lower cost than does the option of not using therapeutic hypothermia.

Criteria for Evidence Grading SBU's Conclusions

Evidence Grade 1 – Strong Scientific Evidence. The conclusion is corroborated by at least two independent studies with high quality, or a good systematic overview.
Evidence Grade 2 – Moderately Strong Scientific Evidence. The conclusion is corroborated by one study with high quality, and at least two studies with medium quality.
Evidence Grade 3 – Limited Scientific Evidence. The conclusion is corroborated by at least two studies with medium quality.
Insufficient Scientific Evidence – No conclusions can be drawn when there are not any studies that meet the criteria for quality.
Contradictory Scientific Evidence – No conclusions can be drawn when there are studies with the same quality whose findings contradict each other.

SBU – The Swedish Council on Technology Assessment in Health Care

SBU is an independent public authority which has the mandate of the Swedish Government to comprehensively assess healthcare technology from medical, economic, ethical, and social standpoints. SBU Alert is a system for identification and early assessment of new methods in health care.

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The complete report is available only in Swedish.

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