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CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Hypothermia for Perinatal Asphyxia: Clinical Effectiveness and Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Research Questions

1. What is the clinical effectiveness on the various applications of hypothermia for neonates/newborns with perinatal asphyxia?
2. What are the evidence-based guidelines regarding the use of hypothermia for neonates/newborns with perinatal asphyxia?

Key Findings

Six randomized controlled trials, five non-randomized studies, and one evidence-based guideline were identified regarding the clinical effectiveness of hypothermia for neonates/newborns with perinatal asphyxia.

Methods

A limited literature search was conducted on key resources PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases and a focused Internet search. Methodological filters were applied to limit the retrieval to health technology assessments, systematic reviews, and meta-analyses, randomized controlled trials, and non-randomized studies, and clinical practice guidelines. The search was limited to English language documents published between January 1, 2013 and April 19, 2018. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Neonates/newborns who have experienced asphyxia during birth (perinatal asphyxia)
Intervention	Therapeutic hypothermia (e.g., cooling, full body cooling)
Comparators	Q1: Different applications of therapeutic hypothermia (e.g., optimal temperature) Q2: No comparator
Outcomes	Q1: Clinical effectiveness (benefit/harm), safety, mortality, preservation of neurodevelopment Q2: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

Six randomized controlled trials, five non-randomized studies, and one evidence-based guideline were identified regarding the clinical effectiveness of hypothermia for neonates/newborns with perinatal asphyxia. No relevant health technology assessments, systematic reviews, or meta-analyses were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Six randomized controlled trials,[1-6] five non-randomized studies,[7-11] and one evidence-based guideline[12] were identified regarding the clinical effectiveness of hypothermia for neonates/newborns with perinatal asphyxia. Detailed study characteristics are provided in Table 2.

Two studies examined timing, duration, and/or temperature of cooling. In one randomized controlled trial,[3] the authors reported no differences between the conventional regimen of cooling for 72 hours at 33.5°C versus increasing the duration of hypothermia to 120 hours and/or decreasing the temperature to 32.0°C. In one non-randomized study,[7] initiating hypothermia at or before 1 hour postnatal was associated with fewer clinical seizures, less abnormal electroencephalogram (EEG) findings, shorter ventilation duration, and shorter hospitalization compared with hypothermia initiated after 1 hour.

Five randomized controlled trials[1-2,4-6] and four non-randomized studies[8-11] were identified regarding the administration of adjunct treatment with hypothermia. One non-randomized study[8] showed positive outcomes associated with the provision of mineral enteral nutrition including reduced length of stay and time to full feeds. In addition, no difference in feeding complications or systemic inflammation compared with unfed infants.[8] A second randomized controlled trial[6] showed premedication with atropine prior to endotracheal intubation during hypothermia increased infants' heart rate and subsequently precipitated higher total dose of sedative morphine. Thus, the authors did not support the ongoing administration of atropine in conjunction with hypothermia.[6]

In two randomized controlled trials[2,4] and one non-randomized study[10] administration of erythropoietin (EPO) during hypothermia was associated with lower brain injury and better neurological function compared with placebo[2,4] and hypothermia alone[10]. Similarly, the authors of a non-randomized[9] study examined the administration of Darbepoetin alfa (comparable biological activity to EPO with extended circulating half-life) in conjunction with hypothermia and observed that the drug was as safe as placebo with pharmacokinetics sufficient for weekly administration.

Hypothermia was demonstrated to be safe with the addition of the anticonvulsant drug topimerate, and was associated with a lower prevalence of epilepsy.[1] However, it did not reduce the frequency of mortality or severe neurological brain injury compared with hypothermia alone in a randomized controlled trial[1]. Another randomized controlled trial[5] showed melatonin may improve survival and brain development compared with

hypothermia alone. Finally, administering gentamicin (antibiotic) with a 24 hour dosing interval was associated with better achievement of target trough concentration compared with a 36 hour interval and provided high peak gentamicin concentration exposure.[5]

One evidence-based guideline was identified regarding the use of therapeutic hypothermia for neurocritical care.[12] The Neurocritical Care Society included recommendations for physicians who have already decided to implement hypothermia in neonates/infants with perinatal asphyxia.[12]

Table 2: Summary of Included Studies on Hypothermia for Perinatal Asphyxia

First Author, Year	Intervention	Comparison	Results	Authors' Conclusions
Randomized Controlled Trials				
Filippi, 2018[1]	Moderate hypothermia +TPM	Moderate hypothermia	No difference between intervention and control for safety (renal, liver, metabolic balance, TPM pharmacokinetics), mortality, severe neurological disability, incidence of MRI injury, blindness, hearing loss, or neurodevelopment at ages 18 to 24 months Lower prevalence of epilepsy in intervention vs. comparison group	Administering TPM in newborns with HIE is safe but does not reduce the frequency of mortality and severe neurological disability
Mulkey, 2017[2]	Hypothermia + EPO	Hypothermia + Placebo	Volume of acute brain injury was lower in intervention vs. comparison group	NR
Shankaran, 2017[3]	Hypothermia 33.5°C for 72 hours	**Comparison 1:** 32.0°C for 72 hours **Comparison 2:** 33.5°C for 120 hours **Comparison 3:** 32.0°C for 120 hours	Death and moderate or severe disability at ages 18 to 22 months (adjusted for centre and level of encephalopathy) did not differ between treatment groups An interaction between temperature and duration of cooling was reported	Cooling term infants with moderate or severe HIE for longer than 72 hours (i.e., 120 hours) and/or lower than *33.5*°C (i.e., 32.0°C) did not reduce death or moderate or severe disability at 18 months of age. These results support the current regimen of cooling for 72 hours at 33.5°C[a]
Wu, 2016[4]	Hypothermia + EPO (1000 U/kg, intravenous) at 1, 2, 3, 5, 7 days of age	Hypothermia + placebo at 1 ,2, 3, 5, 7 days of age	Neonatal deaths did not differ Between intervention and comparison group Global brain injury score from MRI	Administering high doses of EPO to infants with HIE undergoing therapeutic hypothermia may result

Table 2: Summary of Included Studies on Hypothermia for Perinatal Asphyxia

First Author, Year	Intervention	Comparison	Results	Authors' Conclusions
			at Mean 5.1 days was lower in the intervention vs control group Moderate/severe brain injury, subcortical injury was lower in the intervention vs comparison group Cerebellar injury did not differ between intervention and comparison group	in less MRI brain injury and improved 1-year motor function
Aly, 2015[5]	Hypothermia (72 hours) + melatonin (10 mg/kg x 5 doses/day) N = 15	Hypothermia (72 hours) N = 15	Greater increase in melatonin, greater decline in serum nitric oxide, and less decline in plasma superoxide dismutase in intervention vs comparison group At age 2 weeks, fewer seizures on follow-up EEG and less white matter abnormality on MRI were reported for intervention vs comparison group At 6 month follow-up, better survival without neurological or developmental abnormalities was reported for the intervention vs comparison group	Administering melatonin to term infants with HIE may improve brain injury
Gill, 2014[6]	Hypothermia + Xenon (50% Xenon inhalation) N = 32	Hypothermia	"*At postnatal hours five to eight atropine increased HR in a linear regression model (p<0.01). All other independent variables were excluded. Where more than one dose of atropine was given total morphine sedation given up to 8h into the treatment period was significantly higher (p<0.01).*"[6]	Premedication with atropine for endotracheal intubation of term infants undergoing hypothermia significantly increased HR, the main indicator of effective sedation Administering more than one dose of atropine was associated with increased total morphine dose for sedation Administering atropine as part of standard premedication for

Table 2: Summary of Included Studies on Hypothermia for Perinatal Asphyxia

First Author, Year	Intervention	Comparison	Results	Authors' Conclusions
				endotracheal intubation of term neonates undergoing hypothermia should be reconsidered
Non-Randomized Studies				
Timing of Cooling				
Youn, 2016[7]	Early (age ≤1 hour) hypothermia (72 hours) n = 20	Late (age > 1 hour) hypothermia (72 hours) n = 29	Early hypothermia was associated with fewer clinical seizures, less abnormal EEG findings, shorter duration on ventilator, and shorter hospitalization compared with late hypothermia No difference in hypothermia related complications and mortality between groups	Infants with HIE beginning hypothermia at 1 hour of age or earlier had lower Apgar score at 1 min, lower initial calcium level, decreased incidence of clinico-electrical seizures, shorter duration of ventilator support and hospitalization period compared with those beginning hypothermia later than 1 hour
Adjunct Treatment				
Chang, 2018[8]	Hypothermia + mineral enteral nutrition during hypothermia n = 17	Hypothermia without feeding n = 17	Infants receiving mineral enteral nutrition had shorter hospital stay, fewer days receiving parenteral nutrition, shorter time to full oral feeds, and reduced serum IL-12p70 at 24 hours and 96 hours vs comparison group Brain MRI scores did not differ between intervention and comparison group	Providing mineral enteral nutrition to HIE infants undergoing hypothermia was associated with a reduced length of stay and time to full feeds, but did not increase feeding complications or systemic inflammation compared with unfed infants
Baserga, 2015[9]	Hypothermia + Darbe low dose (2 mug/kg) n = 10 Hypothermia + Darbe high dose (10 mug/kg) n = 10	Hypothermia + placebo Dosed within 12 hours of birth (during hypothermia) and at 7 days (during normothermia) n = 10	Adverse events (hypotension, altered liver and renal function, seizures, death) did not differ between intervention and control groups Clearance of Darbe was not significantly different between the doses administered within 12 hours of birth during hypothermia	Administering Darbe with hypothermia was as safe as placebo with pharmacokinetics sufficient for weekly administration

Table 2: Summary of Included Studies on Hypothermia for Perinatal Asphyxia

First Author, Year	Intervention	Comparison	Results	Authors' Conclusions
	Dosed within 12 hours of birth (during hypothermia) and at 7 days (during normothermia)		Clearance of Darbe was longer in the 10 mug/kg vs 2 mug/kg doses administered at 7 days during normothermia	
Zhu, 2015[10]	Hypothermia and conventional treatment + rhuEPO and GM1 n = 34	Hypothermia and conventional treatment + GM1 n = 42	Higher proportion and total effective rate, fewer adverse events (death rate, cerebral palsy), lower invalid ratio, lower awareness, lower muscle tension, lower primitive reflex, and higher increased intracranial pressure recovery time in intervention vs comparison group NBNA scores at 7, 14 and 28 days post-treatment were higher than baseline and increased over time in both groups. Difference between groups NR MDI, PDI and DQ scores at 3, 6 and 12 months post-treatment were higher than baseline and increased in time in both groups. Difference between groups NR	Administering rhuEPO and GM1 treatment in infants with HIE undergoing hypothermia improves short-term clinical effects and long-term neurological symptoms
Frymoyer, 2013[11]	Q24: Hypothermia + empiric gentamicin (5 mg/kg every 24 hours) n = 29	Q36: Hypothermia + empiric gentamicin (5 mg/kg every 36 hours)	Gentamicin clearance between periods did not differ between Q24 vs Q36 Mean gentamicin trough concentration was higher in Q24 vs Q36 Peak gentamicin trough concentration did not differ between groups	Administering 5 mg/kg of gentamicin every 36 hours in neonates with HIE undergoing hypothermia improved achievement of target trough concentration <2 mg/l, and provided high peak gentamicin concentration exposure

APGAR = Appearance, Pulse, Grimace, Activity, Respiration; AUC = Area under the curve; Darbe = Darbepoetin alfa; DQ = Developmental Quotient; EEG = electroencephalography ; EPO = erythropoietin; GM1 = monosialotetrahexosylganglioside; HIE = hypoxic ischemic encephalopathy ; HR = heart rate; MDI = Mental Development Index ; MRI = magnetic resonance imaging; NBNA = Neonatal Behavior Neurological Assessment; NR = not reported; PDI = Psychomotor Development Index; rhuEPO = recombinant human erythropoietin; RR = risk ratio; TPM = topimarate; vs = versus.

[a] Shankaran et al. 2017 was stopped for futility and safety after 364/726 planned infants were enrolled.

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

No literature identified.

Randomized Controlled Trials

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Non-Randomized Studies

Timing of Cooling

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PubMed: PM23702622

Guidelines and Recommendations

12. Madden LK, Hill M, May TL, Human T, Guanci MM, Jacobi J, et al. The Implementation of Targeted Temperature Management: An Evidence-Based Guideline from the Neurocritical Care Society. Neurocrit Care. 2017 Dec;27(3):468-87.
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Appendix — Further Information

Non-Randomized Studies

No Comparator

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