Residual brain injury after early discontinuation of cooling therapy in mild neonatal encephalopathy

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What is already known on this topic

Anecdotal evidence suggests that many cooling centres offer therapeutic hypothermia to babies with mild encephalopathy and often discontinue prior to 72 hours, deviating from the National Institute of Clinical Excellence guidelines.

What this study adds

Brain injury and adverse neurodevelopmental outcomes occur in babies with mild neonatal encephalopathy, after premature cessation of cooling therapy.

ABSTRACT

We examined the brain injury and neurodevelopmental outcomes in a prospective cohort of 10 babies with mild encephalopathy who had early cessation of cooling therapy. All babies had magnetic resonance (MR) imaging and spectroscopy within 2 weeks after birth and neurodevelopmental assessment at 2 years. Cooling was prematurely discontinued at a median age of 9 hours (interquartile range 5-13) due to rapid clinical improvement. Five (50%) had injury on MR imaging or spectroscopy, and two (20%) had an abnormal neurodevelopmental outcome at 2 years. Premature cessation of cooling therapy in babies with mild neonatal encephalopathy does not exclude residual brain injury and adverse long term neurodevelopmental outcomes.

INTRODUCTION

Although therapeutic hypothermia is the standard therapy for moderate and severe neonatal encephalopathy, cooling therapy is increasingly offered to babies with mild encephalopathy[1]. This may be partly due to "therapeutic creep" or the expectation that perhaps these babies could also benefit from cooling, the reassurance of the safety profile of cooling in moderate and severe encephalopathy, or due to the difficulties in accurately measuring the severity of encephalopathy within six hours of birth. Hence, clinicians may err on the side of caution and offer cooling therapy to babies with mild encephalopathy, and then subsequently discontinue cooling if a baby shows rapid clinical recovery.

We examined brain injury and neurological outcomes in babies with mild neonatal encephalopathy, who had early cessation of cooling therapy.

METHODS

We retrospectively identified all babies with mild encephalopathy who were cooled as part of clinical care and who had premature cessation of cooling due to clinical improvement[2], from the study database of the MARBLE study (Magnetic Resonance Biomarkers in Neonatal Encephalopathy). All recruited babies had a) encephalopathy grade assessed before six hours of age using a previously validated neurological examination[3]; b) magnetic resonance (MR) imaging and single voxel thalamic proton spectroscopy (3 Tesla) between 4 to 14 days of age and c) detailed neurological examination at 2 years of age

using Bayley-III® [2] or BAPM/RCPCH working group classification, if Bayley-III® was not available[4].

An MR physicist (PL) post-processed the spectroscopy data using LCModel (LCModel Inc, Oakville, Ontario, Canada, v6.3-1J), and a neonatal neurology consultant (ST) with 8 years of neuroimaging experience reported conventional MR images, masked to the clinical details. The North London Research Ethics Committee and clinical sites approved the MARBLE study (11/H0717/6) and informed parental consent was obtained from parents or legal representatives of the infants.

RESULTS

From a subgroup of 42 babies with mild encephalopathy who were offered cooling as part of clinical care, therapy was prematurely discontinued in 10 (24%) infants (5% of the first 200 babies recruited into the MARBLE study). Clinical characteristics, MR imaging abnormalities and neurodevelopmental outcomes of these 10 babies are given in Table 1. All babies had a normal amplitude integrated electroencephalography (aEEG) at the time of initiation of cooling therapy, which remained normal throughout the cooling period, and had a normal neurological examination at the time of re-warming.

MR imaging was performed at a median age of 6 days (IQR – 5 to 7 days). Five (50%) infants had MR imaging abnormalities – periventricular white matter injury alone (2 babies); subcortical and focal white matter injury (1 baby); severe wide spread white matter injury (1 baby); abnormal signal

intensity in thalami and equivocal loss of T_1 high signal abnormality in the posterior limb of internal capsule (1 baby).

- Three babies (Cases 3, 5 and 6) had white matter injury, of which one baby later had proven sepsis with group-B streptococcus. All of these babies had normal neurodevelopmental outcomes at 2 years of age.
- One baby (Case 4) had white matter injury as well as an elevated thalamic lactate/N-acetyl aspartate ratio (0.35). Additional MR scans at 45 days and 22 months showed persistence of the white matter injury (Figure 1).
- Another baby (Case 8) had white matter injury plus signal abnormalities in the basal ganglia (Figure 1).
- None of the babies had reported hypoglycaemic episodes.

A detailed neurological examination was performed at a median age of 22 months (IQR – 20 to 24 months) and was abnormal for two (20%) of the babies

- None of the babies had cerebral palsy (Gross Motor Function Classification System = 0).
- At 21 months of age, Case 4 had a cognitive composite score of 80 (equivalent developmental age: 16 months), language composite score of 74 (receptive communication equivalent developmental age: 16 months; expressive communication equivalent developmental age: 15 months), and a motor composite score of 82 (fine motor equivalent developmental age: 17 months; gross motor equivalent developmental

age: 16 months). Her gait was not fluent, and she had a persistent adduction of her right thumb.

- At 22 months of age, Case 8 had language delays in expression and receptive communication. He could speak only two words, and did not follow simple instructions or respond to social requests. His neurological examination was normal, except for a poor pincer grasp.

DISCUSSION

Here we report the brain injury and neurodevelopmental outcomes after premature cessation of cooling therapy in a small series of babies with mild encephalopathy.

Discontinuation of cooling therapy due to adverse events or for palliative care is a well-accepted clinical practice, hence we specifically excluded such cases. Discontinuation of cooling in our cohort was driven by a view that therapeutic hypothermia was no longer needed as the baby had already recovered clinically. Uncertainty also existed about whether the infant had fulfilled the cooling criteria in first place (moderate or severe encephalopathy). This often occurs when passive cooling therapy is initiated at a local hospital prior to the referral, followed by a detailed neurological evaluation at the cooling centre, during which the baby no longer exhibits signs of encephalopathy.

It is unclear if brain injury might have been averted if cooling therapy was given up to 72h. Walsh and colleagues from Boston Children Hospital have

recently reported brain injury on MR imaging in 54% of the babies with mild neonatal encephalopathy, despite complete cooling therapy[5]. Nevertheless, in preclinical models, brief hypothermia after hypoxia-ischaemia only postpones brain injury and does not provide any long-lasting neuroprotection[6]. Furthermore, short cooling therapy (48 hours) offers less neuroprotection than standard cooling (72 hours) in fetal sheep model of perinatal encephalopathy[7].

Inflammatory markers are commonly elevated in neonatal encephalopathy even without co-existent infection, and only one baby in our series had proven blood stream positive sepsis (Group B streptococci). Preclinical data suggest that hypothermic neuroprotection may be lost with co-existent gram negative infections, but not with gram positive infections[8]. Hence, lack of neuroprotection in our cohort is unlikely to be due to co-existent perinatal infection.

There are three major limitations of our study. Firstly, the reported incidence of premature cessation of cooling in our study (24%) is likely to be an underestimate, when compared to actual clinical practice. Our babies were part of a multicentre study, and hence may have had closer monitoring. A recent survey in Australia reported a 20% (21/104) incidence of premature cessation of cooling therapy (due to clinical improvement (n=16) or lack of qualification (n=5) in retrospect) in 104 babies who were cooled despite not meeting the cooling criteria[1]. Cooling therapy was also prematurely discontinued in 2% (2/103) of the babies who had originally met the cooling

criteria (at least moderate encephalopathy), due to an apparent clinical improvement. Neuroimaging or neurodevelopmental outcome data were not available in this cohort, nevertheless the authors do raise concerns about such practices. Secondly, although none of our cases seemed to have met the original cooling criteria and had a rapid clinical recovery, the high incidence of brain injury and the adverse neurodevelopmental outcomes in these babies is worrying. This question whether these babies may have in fact suffered moderate (not mild) injury and reflects practical challenges in accurately identifying the severity of encephalopathy within six hours of birth. Finally, we have not compared the outcomes of complete versus incomplete cooling therapy in babies with mild encephalopathy.

The long-held view of uniformly good outcomes in mild encephalopathy is being increasingly challenged in more recent studies. Growing evidence suggests that cognitive impairments and behavioural problems during childhood following mild neonatal encephalopathy are closer to those of children with moderate encephalopathy, than previously thought[8]. Although in three cases the MR imaging abnormalities did not correlate with 2 year outcomes in our series, they could be associated with adverse outcomes during childhood.

Although classical secondary energy failure may not occur in mild encephalopathy, it is possible that perinatal hypoxic injury is a continuum. For example, perinatal asphyxia without encephalopathy leads to a reduction in intelligence quotient compared to healthy peers, and mild, moderate and

severe encephalopathy results increasing severity of long term adverse outcomes. Hypothermia is reported to have marked neuroprotective effect in a recently described pre-clinical model of mild encephalopathy, where the predominant injury was in the white matter[10]. Preclinical studies also report that brain cooling in the absence of perinatal asphyxia, may increase apoptosis[11].

The data presented in this case series suggest that despite clinician perception of clinical recovery, premature cessation of cooling therapy in babies with mild neonatal encephalopathy does not exclude residual brain injury and adverse long term neurodevelopmental outcomes. The creeping introduction of non-standard cooling practices, constantly challenged by residual safety concerns, can only be resolved by large pragmatic trials of cooling in mild encephalopathy. In addition to neurodevelopmental outcome assessments, these studies should also examine the cost benefits, as cooling therapy is expensive and may prolong hospital stay. Such trials are currently in development in the UK and USA.

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Table 1. Clinical characteristics, MR imaging and neurodevelopmental outcomes following premature cessation of cooling therapy

	Case No 1	Case No 2	Case No 3	Case No 4	Case No 5	Case No 6	Case No 7	Case No 8	Case No 9	Case No 10
Delivery	SVD[1]	Instrumental	Em LSCS[2]	Instrumental	Instrumental	Em LSCS	SVD	Instrumental	Em LSCS	Em LSCS
Type of admission	Outborn	Outborn	Outborn	Inborn	Outborn	Outborn	Outborn	Outborn	Inborn	Inborn
Gestational age (weeks+days)	41+2	39+0	40+3	36+5	42+1	41+2	40+3	40	37	41
Birth Weight (g (centile))	3200(9-25)	4530(98-99)	4055(75-91)	3470(91-98)	4260(75-91)	3742(50-75)	3630(50-75)	2990(9)	2640(25-50)	3908(75-91)
Cardiotocography (CTG)	Late deceleration	Normal	Bradycardia	Tachycardia	Bradycardia	Variable deceleration	Bradycardia	Variable deceleration	Bradycardia	Bradycardia
Arterial cord pH	7.2	7.3	6.8	7.1	7.1	6.9	7.2	7.1	6.9	NA
Arterial cord base excess	-10.1	-7.6	Incalculable	-7.9	-8.5	-15.7	-9.2	-9.5	-14.7	NA
Arterial cord pCO2	5.43	5.56	16.2	8.5	8.7	NA	5.33	7.36	12.8	NA
pH on first blood gas	7.2	6.8	7.02	7.3	7.2	7.1	6.9	6.9	7.14	7.05
Base excess on first blood gas	-11.3	-10.2	-13.7	-5.6	-6.8	-9.1	-8.2	NA	-5.2	-13.2
pCO2 on first blood gas	5.13	NA	7.02	5.5	6	5.2	13.7	NA	9.4	NA
Apgar 1 minute	7	0	2	1	4	5	4	3	3	1
Apgar 5 minute	7	0	3	4	8	6	6	6	8	4

Apgar 10 minute			6	0	4	6	10	7	9	8	8	NA
Resuscitation at birth			Intubation	Intubation + ECM[3]	Intubation	Intubation + ECM	Bag and mask	Bag and mask	Bag and mask	Bag and mask	Bag and mask	Intubation
Complications at birth			None	Shoulder dystocia	Failure to progress	Shoulder dystocia	None	MAS[4]	Cord around the neck	Failure to progress	None	MAS
Inotropic support at admission			No	No	Yes	No	No	Yes	No	Yes	No	Yes
Post re-warming inotropic support			No	No	Yes	No	No	Yes	No	Yes	No	Yes
Neurological examination at admission* 0= normal 1= mild 2= moderate 3= severe	LOC[5]		1	1	1	1	1	0	1	1	1	2
	Spontaneous. Activity		1	1	1	1	1	0	1	1	2	1
	Posture		1	1	0	0	1	1	0	0	1	0
	Tone		2	2	2	1	2	1	1	0	1	0
	Reflexes	Moro	1	1	1	1	0	1	1	1	1	1
		Suck	2	1	1	1	1	1	1	1	1	1
	Autonomous System[7]	Pupils	0	0	0	0	0	0	0	0	0	0
		Heart rate	0	0	0	0	0	0	0	0	0	0
		Respir	1	3	0	0	3	3	3	3	3	2

ation											
Rectal temperature before start of cooling (^{0}C)		35.8	36.2	36.8	35.8	34.0	35.5	34.0	NA	35.2	35.0
Age at start of active cooling (hours)		5	4	6	1	2	3	3	7	1	2
Age core target temperature (<34^{0}C) achieved		8	7	9	Never	3	6	4	8	3	4
Age at discontinuation of cooling (hours)**		12	20	13	3	5	10	9	24	3	5
^{6}C-reactive protein at the time of discontinuation of cooling(g/L)		NA	0.5	66	2.3	2.4	23	5	56	0.2	NA
Maximum CRP in first 72 hours of age(g/L)		152	4	284	13	4	62	27	96	0.4	330
Blood/CSF positive culture		No	No	GBS (Blood)	No	No	No	No	No	No	No
CSF microscopy		Negative	Not done	Negative	Not done	Not done	Not done	Not done	Negative	Not done	Negative
MRI	Cortex	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Abnormal	Normal	Normal
	Basal ganglia/thalamus	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Abnormal	Normal	Normal
	White matter	Normal	Normal	Abnormal	Abnormal	Abnormal	Abnormal	Normal	Abnormal	Normal	Normal
	Posterior limb of the	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal

	internal capsule										
[7]Lac/NAA (standard error)		0.07 (0.08)	0.03 (0.03)	0.07 (0.04)	0.35 (0.06)	0.14 (0.03)	0.12 (0.03)	0.18 (0.05)	0.14 (0.04)	0.14 (0.03)	0.15 (0.05)
Neurodevelopmental Outcome at 2 years		Normal	Normal	Normal***	Abnormal	Normal	Normal	Normal	Abnormal***	Normal	Normal

[1]*SVD=spontaneous vaginal delivery;* [2]*Em LSCS = Emergency lower segment cesarean section;* [3]*ECM = external cardiac massage;* [4]*MAS = Meconium aspiration syndrome;* [5]*LOC= Level of consciousness;* [6]*tLac/NAA: total lactate/N acetyl aspartate (>0.3 is associated with adverse neurological outcome); GBS: Group B Streptococcus..*

**To classify as mild encephalopathy, babies had at least one abnormality in the neurological examination, but no evidence of moderate or severe encephalopathy (which requires at least 3 moderate or severe abnormalities)*

***Rewarming rate set at 0.25 ^{0}C per hour using Criticool or Tecotherm Neo*

****Only detailed neurological examination without Bayley-III® was performed.*

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