For the future for the children

子ども達の未来はわたし達の未来

Long-term outcome after therapeutic hypothermia for neonatal hypoxic ischemic

Masaki Shimizu, MD PhD
Division of Neonatology
Saitama Children's Medical Center

ILCOR
International Liaison Committee On Resuscitation

CoSTR2010 Guideline

TREATMENT RECOMMENDATION:

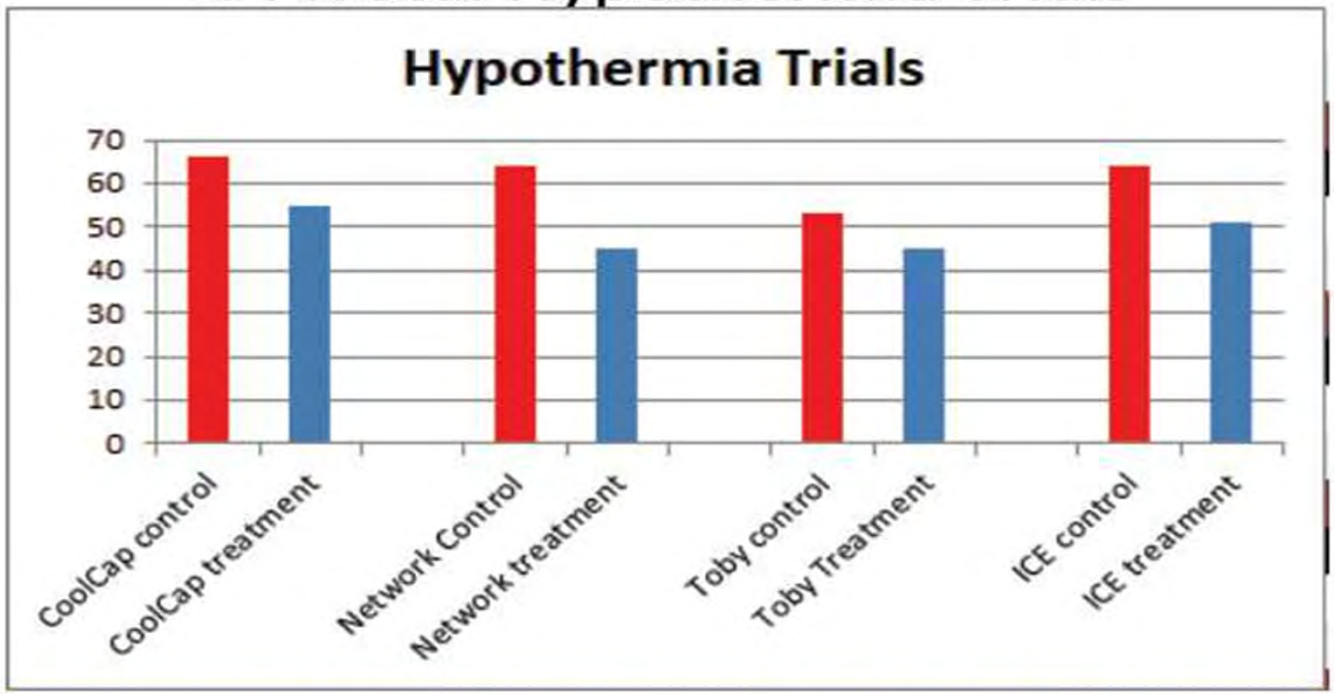
Newly born term infants with evolving moderate/severe hypoxic ischemic encephalopathy should be offered therapeutic hypothermia.

Whole body cooling and selective head cooling are both appropriate strategies. Treatment should be consistent with the protocols used in the RCTs; i.e.:

- Commence within 6 h of birth
- Continue cooling for 72 h
- Rewarm over at least 4 h
- Carefully monitor for known adverse effects of cooling – thrombocytopenia and hypotension

Neonatal brain hypothermia

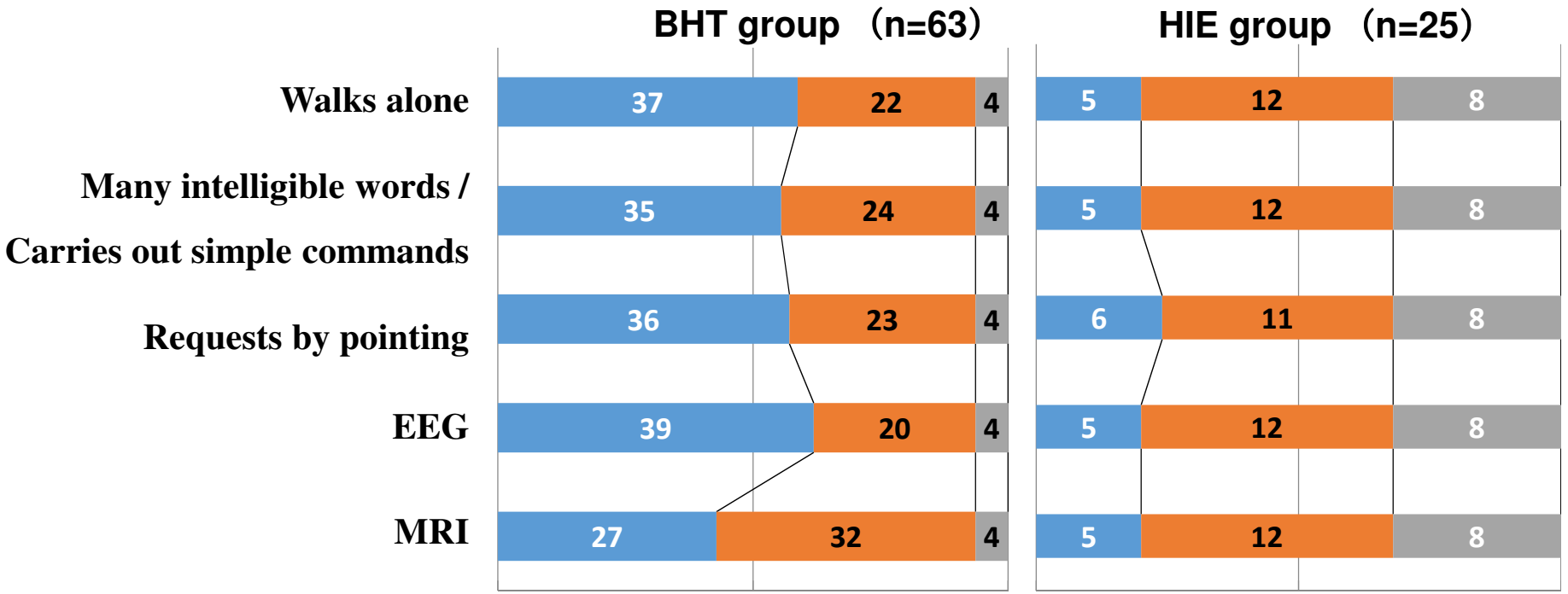
Primary Outcomes
4 Pivotal Hypothermia Trials



% of kids in control groups w/ primary outcomes in red bars, cooled kids are blue bars

Primary Outcomes: Mortality, Moderate/Severe disability

Mortality and Neurological Prognosis



	Good	Disability	Death
BHT group	35 (55.6%)	24 (38.1%)	4 (6.3%)
HIE group	2 (8.0%)	15 (60.0%)	8 (32.0%)

P=0.010

Long-term outcome after therapeutic hypothermia for neonatal hypoxic ischemic

Objective

- evaluate the neurological prognosis
- cognitive evaluation at 5 to 7 years of age
- treated with hypothermia for neonatal HIE

Subjects

- 66 infants received TH for moderate or severe HIE
- the Saitama Children's Medical Center from 1999 to 2008
  (the TH group)

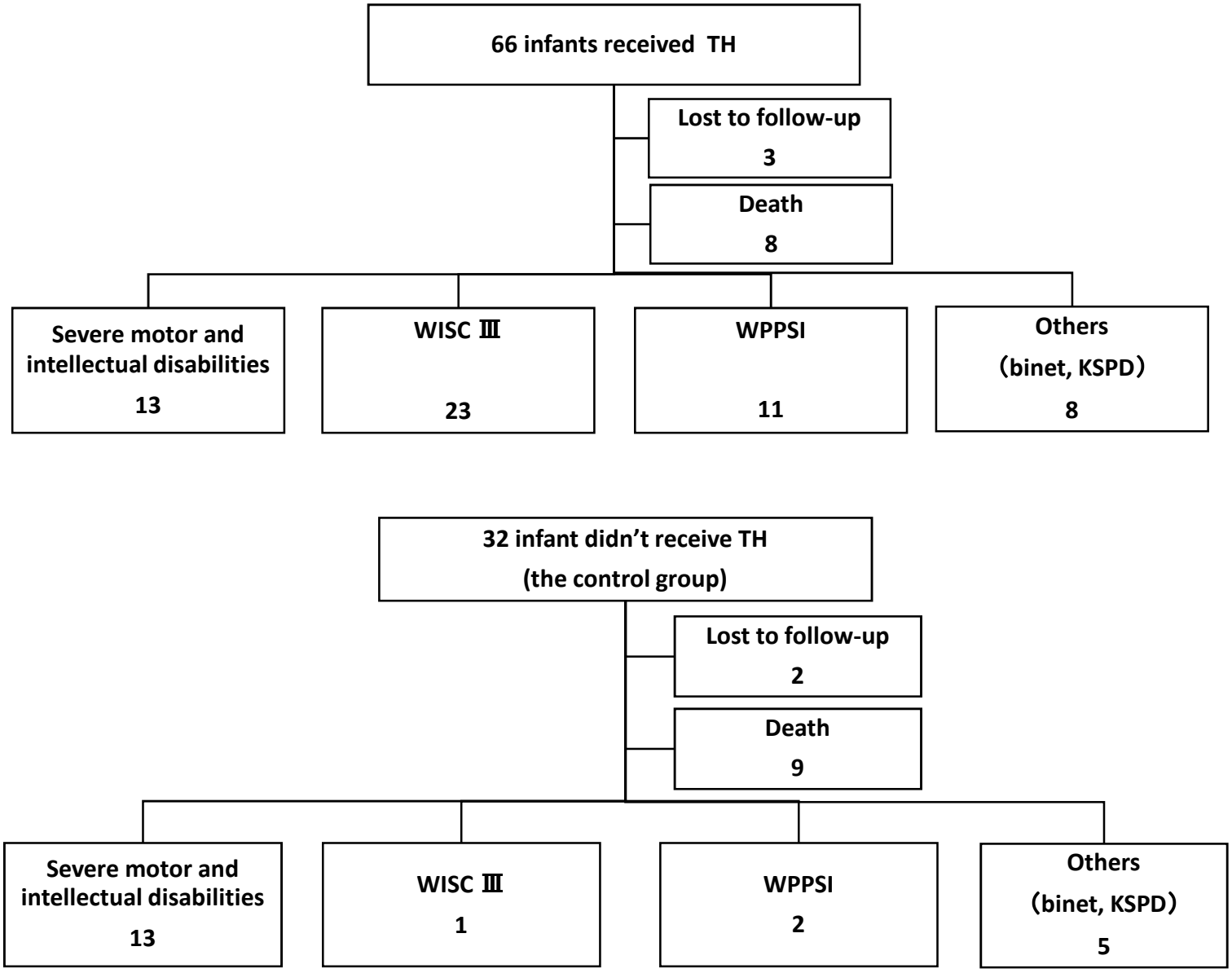
Methods

- Prognosis was retrospectively investigated.
- IQ scores：measured at 5 to 7 years of age by clinical psychologists
- the Wechsler Intelligence Scale for Children-III (WISC-III)
- the Wechsler Preschool and Primary Scale of Intelligence (WPPSI)
- Kyoto Scale of Psychological Development (KSPD)
- children who had received conventional care before the introduction of TH (the control group)

Classifications of for Neurological outcomes

The neurological evaluation	
Death	**The death within 5years**
Severe disability	**CP (GMFCS Ⅳ, Ⅴ) or DQ/IQ 55>**
Moderate disability	**CP(GMFCS Ⅰ, Ⅱ, Ⅲ) or Hearing loss or EPI or DQ/IQ;55-69**
Mild disability	**DQ /IQ;70-84 and no complications**
Normal	**DQ/IQ;85≦ and no complications**
CP ; cerebral palsy GMFCS ; Gross Motor Function Classification System Epi ; Epilepsy DQ ; developmental quotient IQ ; intelligence quotient	

Study profile



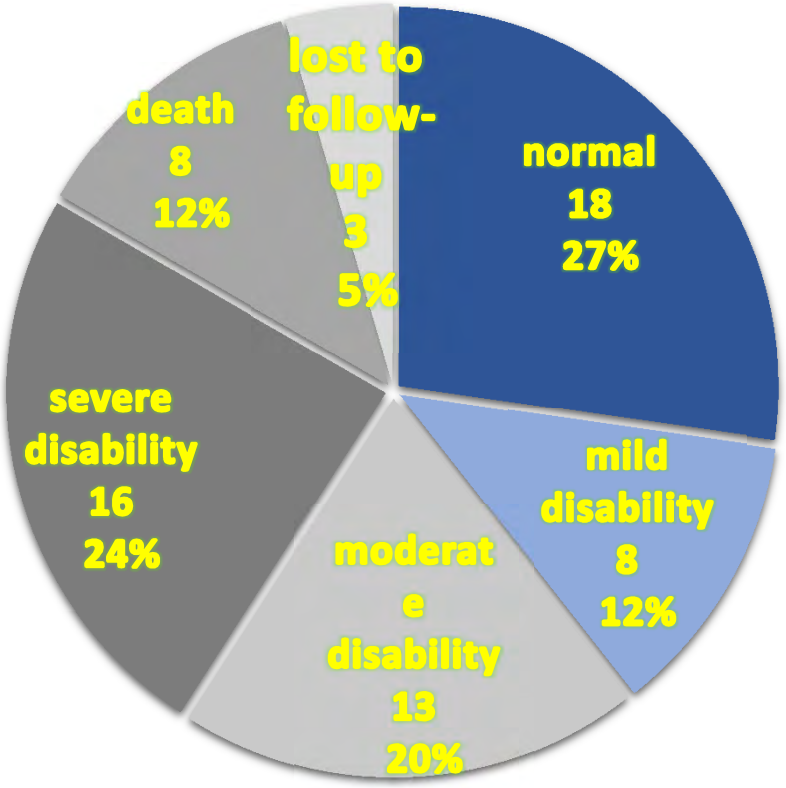
Baseline characteristics of the TH group vs. the control group

	TH (n=63)	Control (n=30)	
Gestational age(w)	38.9±2.1	38.6±2.3	p=0.47
Birth Weight(g)	2825±452	2907±604	p=0.56
Apgar score at 1min	2.0±1.4	2.8±1.9	p=0.1
Apgar score at 5min	3.6±2.2	4.3±2.2	p=0.08
Male sex(%)	27 (12)	13 (43)	p=0.96
Sarnat's Score Ⅲ(%)	23 (37)	12 (40)	p=0.74
Blood pH (at admission)	7.19±0.2	7.22±0.15	p=0.5
Lactate (at admission) (mmol/dl)	14.3±5.8	14.4±8.4	p=0.75
Base deficit (at admission) (mmol/L)	-15.6±7.4	11.4±8.8	p=0.04

Neurodevelopmental outcomes at 5-7years (n=66)

n=66

CP 16 (25%)
DQ/IQ 70> 37 (59%)
Hearing loss 3 (5%)
PDD-NOS 2 (3%)



Death	The death within 5years
Severe disability	CP(GMFCSⅣ, Ⅴ) or DQ/IQ 55>
Moderate disability	CP(GMFCS Ⅰ, Ⅱ, Ⅲ) or Hearing loss or EPI or DQ/IQ;55-69
Mild disability	DQ /IQ;70-84
Normal	DQ/IQ;85≤

PDD - NOS: Pervasive Developmental Disorder-Not Otherwise Specified

Predictive factor for neurological prognosis at 5-7years of age

	Normal ＋Mild disability [a] n=26	Moderate disability [b] n=13	Severe disability + death [c] n=24	p<0.05 a-b : * a-c : * * b-c: * * *
Gestational age(w)	38.8±2.1	39.2±1.7	39.0±2.3	NS
Birth Weight(g)	284±428	2841±498	2795±470	NS
Apgar score at 1min	2.8±1.5	1.8±1.1	1.5±1.2	p=0.01* *
Apgar score at 5min	4.7±2.1	3.7±1.6	2.5±2.0	p=0.003* *
Male sex(%)	14 (54)	9 (70)	11 (52)	NS
Sarnat's ScoreⅢ(%)	5 (19)	2 (20)	16 (67)	p =0.0007* * p=0.002* * *
Blood pH at admission	7.27±0.2	7.15±0.1	7.12±0.2	NS
Lactate at admission (mmol/dl)	12.5±4.8	14.8±5.4	17.1±8.8	p=0.02* *
Base deficit at admission (mmol/L)	−12.0±7.4	−17.6±6.4	−18.2±6.5	p=0.01* *
Abnormal Brain MRI at discharge (%)	8 (31)	9 (69)	21 (100)	p=0.02* p<0.0001* * p=0.007* * *
Abnormal Brain MRI at 18mo (%)	4 (15)	8 (62)	17 (100)	p=0.003* p<0.0001* * p=0.01* * *
EEG (at admission) Flat or Burst Suppression (%)	5 (22)	2 (17)	16 (67)	p=0.002* * p=0.005* * *

Neurodevelopmental outcomes at 5-7years compered the control group

	TH group n=63	Control group n=30	P value
Death or Severe disability (%)	24 (38)	22 (73)	0.002
Death(%)	8 (13)	9 (30)	0.04
Severe disability (%)	16 (25)	13 (43)	0.08
Moderate disability(%)	13 (24)	2 (7)	0.09
Mild disability(%)	8 (12)	3 (10)	0.7
Normal (%)	18 (27)	3 (10)	0.04
Cerebral Palsy (%)	16 (25)	12 (40)	0.15
Abnormal Brain CT/MRI at discharge (%) （n=53/28）	38 (63)	24 (90)	0.03

The result of Wechsler intelligence tests
for normal/mild disability children (n=25)

WISC-Ⅲ/WPPSI :20/5	Average (range)
Test age (years)	6.3±1.2 (5-10.2)
Full IQ (FIQ)	94±17.6 (73-150)
Verbal IQ (VIQ)	95 ±18.3 (70-140)
Performance IQ (PIQ)	94 ±15.2 (65-125)

VIQ/PIQ discrepancy

Average(SD)	**15.6 (±9.5)**		**Mild disability**
15≦	**13 (52%)**	**VIQ<PIQ 6**	**4**
10～14	**6 (30%)**	**VIQ<PIQ 3**	**1**
9≧	**6 (24%)**		**3**

IQ scores by WISC Ⅲ or WPPSI were obtained for 25 children with normal or mild disability.
In 13 of the 25 children (52%), a gap of 15 points or more between VIQ and PIQ was observed.

Baseline characteristics of normal/mild disability children with discrepancy

VIQ/PIQ discrepancy	15≦ (n=13)	10-14 (n=6)	10> (n=6)	P value
Gestational age(w)	39.7±1.5	38.1±2.3	37.4±2.0	ns
Birth Weight(g)	3037±313	2621±431	2631±528	ns
Apgar score at 1min	2.4±1.5	2.8±1.6	3.5±1.6	ns
Apgar score at 5min	4.9±1.7	3.7±2.5	4.8±2.6	ns
Male sex(%)	8 (61)	3 (50)	2 (40)	ns
Sarnat's ScoreⅢ(%)	3 (23)	2 (33)	1 (17)	ns
Blood pH (at admission)	7.32±0.2	7.27±0.2	7.27±0.2	ns
Lactate (at admission) (mmol/dl)	-9.6±5.7	-13.3±8.5	-12.2±11.0	ns
Base deficit (at admission) (mmol/dl)	11.2±3.4	13.5±6.3	12.7±5.8	ns
Abnormal Brain MRI at discharge (%)	4/12 (33)	2/6 (28)	2/6 (33)	ns
Abnormal Brain MRI at 18mo (%)	2/11 (18)	1/6 (17)	1/6 (17)	ns
EEG (at admission) Flat or Burst Suppression (%)	2/10 (20)	1/6 (17)	2/6(30)	ns

Discussion

- In this study, the results of the WISC-III/WPPSI in the TH group with IQ ≥ 70 indicated that approximately 50% of the children had a large gap in their VIQ and PIQ scores. This suggested cognitive function imbalances that could affect studying at school. Children who received brain hypothermia require a longer-term follow-up to study its effects on cognitive outcome.
- This study suggested that the introduction of TH for neonatal HIE improved motor function prognosis by protecting the cerebral cortex. However, as impairment of the basal ganglia, which governs cognitive function, appears to have persist, further treatment strategies need to be developed.

Thank you for your attentions