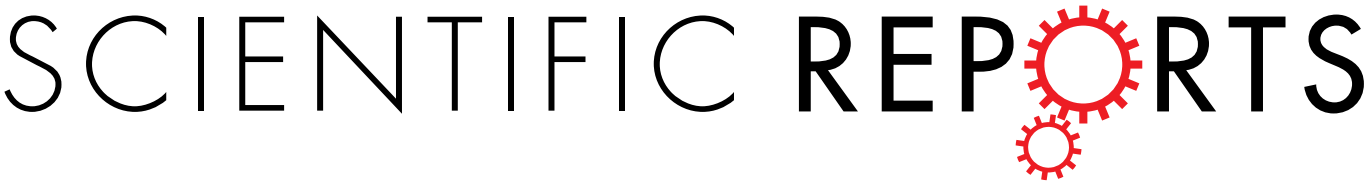

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Therapeutic hypothermia for neonatal encephalopathy: a report from the first 3 years of the Baby Cooling Registry of Japan

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Therapeutic hypothermia is recommended for moderate and severe neonatal encephalopathy, but is being applied to a wider range of neonates than originally envisaged. To examine the clinical use of therapeutic hypothermia, data collected during the first 3 years (2012–2014) of the Baby Cooling Registry of Japan were analysed. Of 485 cooled neonates, 96.5% were ≥36 weeks gestation and 99.4% weighed ≥1,800 g. Severe acidosis (pH < 7 or base deficit ≥16 mmol/L) was present in 68.9%, and 96.7% required resuscitation for >10 min. Stage II/III encephalopathy was evident in 88.3%; hypotonia, seizures and abnormal amplitude-integrated electroencephalogram were observed in the majority of the remainder. In-hospital mortality was 2.7%; 90.7% were discharged home. Apgar scores and severity of acidosis/encephalopathy did not change over time. The time to reach the target temperature was shorter in 2014 than in 2012. The proportion undergoing whole-body cooling rose from 45.4% to 81.6%, while selective head cooling fell over time. Mortality, duration of mechanical ventilation and requirement for tube feeding at discharge remained unchanged. Adherence to standard cooling protocols was high throughout, with a consistent trend towards cooling being achieved more promptly. The mortality rate of cooled neonates was considerably lower than that reported in previous studies.

Hypoxic-ischaemic encephalopathy of the newborn remains an important cause of mortality and morbidity in newborns[1]. The results of large randomised controlled trials (RCTs) indicate that therapeutic hypothermia (TH), using either selective head cooling (SHC) or whole body cooling (WBC), reduces the incidence of death and severe disability following neonatal encephalopathy[2–8]. Based on these studies, TH initiated within 6 h of birth has been recommended since 2010 as the standard of care for newborn infants ≥36 weeks gestation and ≥ 1,800 g birth weight with moderate to severe neonatal encephalopathy[9,10]. Now that the technique has become a routine part of clinical practice, it is expected that TH will be used in a broader range of neonates than the

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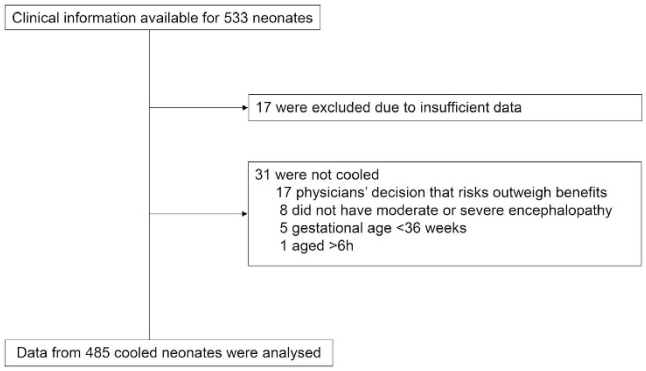

Figure 1. Profile of the registry.

recommendations suggest[11]. Indeed, a survey conducted in 330 North American neonatal intensive care units demonstrated that approximately 30% of the units administered TH to neonates ≤35 weeks gestation[12]. An extensive registry established in the United Kingdom for the TOBY Study suggested the presence of "therapeutic drift", whereby TH was being used outside the originally intended indications. In approximately 10% of neonates registered between December 2006 and July 2011, cooling commenced >6 h after birth, and the extent of birth asphyxia suggested by initial blood base deficits and amplitude-integrated encephalography (aEEG) patterns gradually became less severe over the study period[4].

Previously in Japan, the use of TH as a clinical strategy outside clinical trials had been determined by empirical rather than evidence-based indications and protocols[13]. To ensure evidence-based best practice, a series of substantive alterations were undertaken in 2010[14] to coincide with the release of the revised Consensus Statement and Treatment Recommendation on Cardiopulmonary Resuscitation (CoSTR)[9]. Owing to the nationwide campaign, adherence to evidence-based cooling protocols improved from 20.7% to 94.7% in less than 3 years[14].

To further examine and monitor the use of TH in neonates, an online case registry was established in January 2012. The aims of this study were to examine adherence to the standard cooling protocol and illuminate changes in cooling practice during the first 3 years of the case registry.

Results

Clinical characteristics of registered patients. Over the 3-year period, the clinical information of 533 infants was submitted from 100 units; 17 were excluded from the analysis because of missing data (Fig. 1). Thirty-one neonates of gestational age 38.7 ± 2.0 weeks and birth weight 2,889 ± 509 g were considered for TH, but were not cooled because: (i) physicians considered that the risk of TH outweighed the potential benefits because of the patient's clinical condition (n = 17); (ii) encephalopathy was mild at the time of admission (n = 8); (iii) gestational age was <36 weeks (n = 5), or (iv) the neonate was aged >6 h (n = 1). The remaining 485 neonates of gestational age 38.7 ± 3.5 weeks and birth weight 2,862 ± 465 g underwent TH (Table 1). Data from non-cooled neonates were not subject to further analysis, and the proportions presented in the following section are calculated based on the 485 cooled neonates unless otherwise stated.

Indications for cooling. Seventeen neonates (3.5%) were <36 weeks gestation, and three (0.6%) weighed <1,800 g. Apgar scores at 10 minutes were recorded for 369 neonates; scores ≤5 were present in 220 cases (59.6%). Severe acidosis (pH < 7 or base deficit ≥16 mmol/L) for the cord or first blood gas analysis within 1 h of birth was confirmed in 334 neonates (68.9%). The majority (469 neonates, 96.7%) had required persistent resuscitation for >10 minutes after birth. Four neonates (0.8%) neither required continuous resuscitation for >10 minutes, nor had severe acidosis or 10-minute Apgar scores ≤5; however, two had clinical seizure activity. Of 471 neonates with completed Sarnat encephalopathy stage data at admission, 288 (61.1%) and 128 (27.2%) neonates had stage II and III neonatal encephalopathy, respectively. Fifty-five (11.7%) had stage I encephalopathy; however, abnormal primitive reflexes (for example weak/absent sucking, rooting and the Moro reflex) were observed in all 55 cases, and signs suggestive of moderate encephalopathy, such as moderate/severe hypotonia (n = 21), clinical seizure activity (n = 4) and moderately/severely abnormal aEEG (n = 4) were observed in the majority. An aEEG was obtained in 295 (60.8%) and 201 (41.4%) neonates at admission and on the day of rewarming, respectively. The use of aEEG was more common for neonates who were cooled by WBC than those cooled by SHC at admission (66.1% for WBC *versus* 53.9% for SHC, $P = 0.016$) and on the day of rewarming (49.8% for WBC *versus* 30.0% for SHC, $P < 0.001$).

Therapeutic hypothermia. In 408 neonates with temperature data available at admission, mean body temperature was 35.9 ± 1.5 °C (Table 2). Body temperature at admission was ≥38 °C in 14 (3.4%) neonates, whereas hypothermia (<35 °C) was recorded in 73 cases (17.9%, Fig. 2). In 468 cases with data available, cooling was commenced on average 222 ± 93 minutes after birth and 105 ± 87 minutes after admission. Cooling was commenced within 6 h of birth in 452 cases (96.6%). After the commencement of cooling, the target core body temperature was achieved in an average of 94 ± 154 minutes, leading to the completion of cooling initiation on average 312 ± 183 minutes after birth.

Variables	2012	2013	2014	Entire period
Number of registrations	186	154	145	485
Centres registering cases	73	71	59	100
Maternal				
Age (year)	31.7 ± 5.1	32.4 ± 5.2	31.5 ± 5.6	31.8 ± 5.3
Primigravida	67 (36.2)	60 (39.7)	50 (35.0)	177 (37.0)
Emergency delivery*	136 ± 73.1	105 ± 68.2	109 ± 75.2	350 ± 72.2
Neonatal				
Gestational age (week)	39.0 ± 1.7	38.7 ± 3.5	38.3 ± 4.9	38.7 ± 3.5
Birth weight (g)	2839 ± 460	2904 ± 443	2847 ± 495	2862 ± 465
Outborn	132 (71.0)	110 (71.4)	100 (69.0)	342 (70.5)
Apgar score				
1 min.	1 {1–3}	2 {1–3}	1 {1–2}	1 {1–3}
5 min.	4 {2–5}	3 {2–5}	3 {2–5}	4 {2–5}
10 min.	5 {3–6}	5 {3.5–7}	5 {3–7}	5 {3–7}
Cord or first blood gas <1 h of birth				
pH	6.95 ± 0.21	6.95 ± 0.22	6.92 ± 0.20	6.94 ± 0.21
Base deficit (mmol/L)	14.8 ± 11.1	14.0 ± 0.18	15.1 ± 10.1	14.6 ± 10.5
Sarnat encephalopathy stage at admission				
Stage I	20 (11.2)	12 (8.0)	23 (16.2)	55 (11.7)
Stage II	110 (61.5)	97 (64.7)	81 (57.0)	288 (61.1)
Stage III	49 (27.4)	41 (27.3)	38 (26.8)	128 (27.2)
Thompson encephalopathy score at admission				
	11 {8–15}	11 {9–15}	11 {7–15}	11 {8–15}

Table 1. Maternal and neonatal baseline characteristics by year of registration. Data are processed excluding missing values and are presented as number (%), mean ± standard deviation or median {inter-quartile range}. *Including emergency caesarean, forceps and vacuum-assisted vaginal delivery.

Variables	2012	2013	2014	Entire period
Selective head cooling	101 (54.6)	54 (36.0)	26 (18.4)	181 (38.0)
Whole body cooling	84 (45.4)	96 (64.0)	115 (81.6)*	295 (62.0)
Body temperature at admission (°C)	36.0 ± 1.1	35.9 ± 1.9	35.8 ± 1.4	35.9 ± 1.5
Time of admission after birth (min.)	102 ± 73	114 ± 88	107 ± 90	107 ± 83
Commencement of cooling after admission (min.)	101 ± 80	104 ± 94	113 ± 88	105 ± 87
Commencement of cooling after birth (min.)	215 ± 92	226 ± 93	225 ± 93	222 ± 93
Time to reach the target temperature after the commencement of cooling (min.)	104 ± 141	110 ± 216	66 ± 71**	94 ± 154
Time to reach the target temperature after birth (min.)	316 ± 179	331 ± 234	288 ± 125	312 ± 183

Table 2. Initiation of cooling by year of registration. Values are shown as number (%) or mean ± standard deviation. *$P < 0.001$ from the chi-squared test with the Bonferroni correction, compared with 2012. **$P = 0.004$ from the analysis of variance and Dunnett's test, compared with 2012. Target core-body temperatures were 34.5 ± 0.5 °C for selective head cooling and 33.5 ± 0.5 °C for whole body cooling.

Among 476 neonates with complete data recorded over the first 4 days, SHC and WBC were used in 181 (38.0%) and 295 (62.0%) neonates, respectively. The mean core body temperature during cooling (from 6–72 h after the commencement of cooling) was 34.0 ± 0.6 °C and 33.7 ± 0.5 °C for SHC and WBC, respectively. The mean heart rates during SHC and WBC were 114 ± 15 beats/min and 112 ± 14 beats/min, respectively, and the mean blood pressure was 49 ± 6 mmHg and 48 ± 6 mmHg, respectively (Supplemental Table 1).

Adjuvant neuroprotective therapies were used in 148 cases (30.5%) using magnesium sulphate (n = 114), erythropoietin (n = 16), edaravone (n = 12), osmotic diuretics (n = 8), phenobarbital (n = 5) and/or ulinastatin (n = 3).

Outcome at discharge. Of 474 neonates whose short-term outcome was confirmed, 430 (90.7%) were discharged home after 59.3 ± 122.3 days, 13 (2.7%) died before discharge and 31 (6.5%) were referred to other hospitals or transitional centres for further medical care (Table 3). The majority (86.3%) were successfully weaned

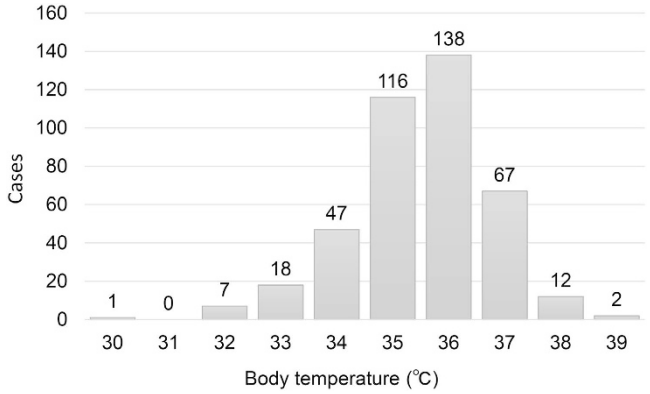

Figure 2. Mean body temperature at admission. The mean body temperature at admission was 35.9 °C ±1.5 °C (mean ± standard deviation). Body temperature was ≥38 °C, <35 °C and <33 °C in 14 (3.4%), 73 (17.9%) and eight neonates (2.0%), respectively. Data are based on the 408 neonates whose body temperature was recorded at admission.

Variables	2012	2013	2014	Entire period
Adverse events during hospital stay	n = 186	n = 154	n = 145	n = 485
Hypotension†	64 (34.4)	48 (31.2)	57 (39.3)	169 (34.8)
Clinically diagnosed seizures	39 (21.0)	38 (24.7)	43 (29.7)	120 (24.7)
Coagulation disorders††	17 (9.1)	25 (16.2)	22 (15.2)	64 (13.2)
Arrhythmia‡	2 (1.1)	3 (1.9)	2 (1.4)	7 (1.4)
Hypoglycaemia‡‡	1 (0.5)	2 (1.3)	2 (1.4)	5 (1.0)
Culture-positive septicaemia	0 (0.0)	2 (1.3)	2 (1.4)	4 (0.8)
Subcutaneous fat necrosis	1 (0.5)	1 (0.6)	0 (0.0)	2 (0.4)
Short-term outcome during hospital stay*	n = 184	n = 150	n = 140	n = 474
Successful weaning from mechanical ventilation	156 (84.8)	135 (90.0)	118 (84.3)	409 (86.3)
Duration of mechanical ventilation (day)**	11.2 ± 31.8	9.2 ± 13.0	13.3 ± 31.2	11.2 ± 27.0
Establishment of full oral feeding (day)**	15.9 ± 16.8	14.1 ± 8.9	13.1 ± 8.0	14.5 ± 12.4
Duration of hospital stay (day)*	72.7 ± 167.4	47.1 ± 69.6	54.5 ± 90.0	59.3 ± 122.3
Status of discharge*	n = 184	n = 150	n = 140	n = 474
Death before discharge	5 (2.7)	3 (2.0)	5 (3.6)	13 (2.7)
Discharged home	168 (91.3)	137 (91.3)	125 (89.3)	430 (90.7)
Transferred to a different hospital	11 (6.0)	10 (6.7)	10 (7.1)	31 (6.5)
Dependence on tube feeding	38 (20.7)	22 (14.7)	28 (20.0)	88 (18.6)
Dependence on respiratory support	19 (10.3)	12 (8.0)	15 (10.7)	46 (9.7)

Table 3. Short-term outcomes and adverse events by year of registration. Values are shown as the number (%) or mean ± standard deviation. *Excluding neonates whose clinical outcome has not been confirmed. **Excluding neonates who were mechanically ventilated or fed through a tube at discharge. †Defined as persistent hypotension with mean blood pressure ≤40 mmHg. ††Defined as clinical bleeding, thrombocytopaenia and/or abnormal coagulation studies. ‡Defined as persistent or recurrent arrhythmia, excluding sinus bradycardia. ‡‡Defined as blood glucose <45 mg/dL.

from mechanical ventilation after 11.2 ± 27.0 days, whereas 46 (9.7%) required persistent mechanical ventilation, even at the time of discharge or transfer to another institution. Full oral feeding was established in 386 (81.4%) cases during initial hospital admission.

Adverse events. Serious adverse events were observed in 371 cases, and consisted of: hypotension (34.8%); clinically diagnosed seizures (24.7%); coagulation disorders (13.2%); arrhythmia (1.4%); hypoglycaemia (1.0%); septicaemia (0.8%) and subcutaneous fat necrosis (0.4%) (Table 3).

Changes in practice over 3-year study period. Apgar score at 10 minutes, cord or first blood pH and base deficit, Sarnat encephalopathy stage and Thompson encephalopathy score at admission did not change significantly in the first 3 years of the registry (Table 1). Similarly, body temperature at admission and the time to start cooling (after birth) remained unchanged over the 3 years (Table 2). In contrast, the mean time to reach the target temperature after initiation of cooling fell significantly from 104 ± 141 minutes in 2012 to 66 ± 71 minutes

in 2014 ($P = 0.004$). The proportion undergoing SHC fell and the proportion undergoing WBC rose over time, so that WBC accounted for 81.6% of cases in 2014 ($P < 0.001$ compared with 2012). In 2012, the proportion of neonates undergoing aEEG at admission was 44.1%, with 27.4% undergoing aEEG on the day of rewarming, which increased to 79.3% and 46.3%, respectively, in 2014 (both $P < 0.001$).

Short-term outcomes, including duration of mechanical ventilation, duration of hospital stay, requirement for tube feeding at discharge, requirement for mechanical ventilation at discharge or referral to other centres, and mortality rate during the initial hospital stay remained unchanged over the study period (Table 3).

Discussion

Adherence to standard cooling protocols was maintained at a high level in Japan, even after the conclusion of the nationwide implementation campaign that ran between 2010 and 2012[14]. During the first 3 years of the Baby Cooling Register, there was a substantial change in cooling technique from SHC to WBC. A consistent trend towards more prompt initiation of cooling was also observed. The mortality rate of cooled neonates before discharge was 2.7%, substantially lower than previous clinical trials and registers[2–4].

Despite the established efficacy of TH for neonatal encephalopathy[15], approximately 40% of neonates do not respond, and consequently many will go on to develop permanent neurological impairments or succumb[16]. To further improve the cooling protocol, a recent large-scale RCT[17] examined the potential benefits of deep (32.0 °C) and prolonged (120 h) hypothermia; however, there was a trend towards increased short-term mortality rates with deep/prolonged cooling compared with the current standard cooling protocol. Several other RCTs of TH with revised cooling indications/protocols are underway, but further improving the therapeutic efficacy of TH might be challenging considering the body of clinical evidence that has informed the choice of the current standard cooling criteria and protocol. Nevertheless, large-scale clinical databases of cooled neonates can now be established relatively easily, which may help identify novel techniques or refine cooling strategies that further improve outcomes in cooled neonates. The UK TOBY Register and the Vermont Oxford Network Neonatal Encephalopathy Registry were the first major attempts to collect a large-scale clinical dataset[18,19]. Although these registries recorded that the standard TH protocol was generally followed outside RCTs, the application of TH to neonates with less severe asphyxia, to those <36 weeks gestational age and/or >6 h after birth, was already evident. A more recent survey in California found that the proportion of neonates with mild encephalopathy who were cooled increased from 38% to 55% between 2010 and 2012[20].

In contrast with the therapeutic drift observed in Western countries[18–20], we found that, even up to 4 years after the initial recommendation of TH for neonatal encephalopathy[9], the standard cooling criteria and protocol were followed in most neonatal care centres in Japan. When TH was newly recommended as a standard of care in 2010[9], a substantial proportion of Japanese neonatal intensive care centres had already started cooling encephalopathic neonates according to empirically-acquired cooling indications and protocols[13]. To disseminate evidence-based best practice for TH for newborn infants, a dynamic nationwide campaign was conducted between 2010 and 2012, leading to a dramatic improvement in adherence to the standard cooling criteria and protocol[14]. The Baby Cooling Registry of Japan was opened in 2012 to disseminate evidence-based cooling practice by monitoring the clinical use of TH, and by giving feedback to participating units. As well as ensuring adherence to the standard cooling protocol, we found that cooling was initiated more promptly over the first 3 years of the registry, which may explain the increase that we observed in the number of neonates in whom TH was achieved within the therapeutic time window.

Our study also identified an increase in the use of WBC over time. Although SHC is non-inferior to WBC in its therapeutic benefit, it is more difficult to perform cot-side examinations, such as cranial ultrasound and electroencephalogram, when SHC is used. This might explain our observation that a smaller proportion of SHC-cooled neonates underwent aEEG compared with those cooled by WBC. Moreover, the concept of simultaneous head cooling and body warming is sometimes misleading. Indeed, our previous nationwide survey in Japan found that a substantial proportion of units were undertaking SHC using relatively warm cap temperatures >25 °C, which were servo-controlled with reference to the nasopharyngeal temperature[13]. As this empirical protocol was in widespread use in Japan by 2010, the Neonatal Hypothermia Task Force Japan decided to promote WBC rather than disseminating the correct protocol for SHC. This is likely to have contributed to the reduction in the use of SHC over time.

With regard to the short-term outcome of cooled neonates, it is known that the mortality rates of cooled neonates vary between RCTs, as seen in the CoolCap (33%)[2], NICHD (24%)[3] and UK TOBY (26%) studies[4], despite the use of similar inclusion criteria. A more recent clinical study showed a relatively lower short-term mortality rate of 7% in neonates who were randomised to WBC to 33.5 °C for 72 h[17]. In our cohort, the mortality rate of cooled neonates was 2.7%. This might not fully be explained by the difference in severity of neonatal encephalopathy considering that standard cooling indications were followed closely. Global comparative studies are needed to illuminate the factors associated with short- and long-term outcomes of cooled neonates.

Several limitations of the current study must be acknowledged. First, we were not able to analyse follow-up data of our cohort of cooled neonates. For most participating units, only one or two cases were cooled each year, which will likely influence the level of experience within each unit, and the subsequent outcome of cooled neonates. The Baby Cooling Registry of Japan is currently collecting data after hospital discharge to investigate the outcome of neonates cooled in different types of units using various therapeutic regimens. Second, although we provided reference values for the heart rate and blood pressure in neonates cooled with SHC and WBC, we did not collect information regarding the use of inotropes. Third, the number of registered cases is smaller than might be expected from the approximately 1,000,000 births in Japan *per annum* that were registered between 2012 and 2014. We would expect to see 1,000–2,000 cases of neonatal encephalopathy each year given that the incidence of neonatal encephalopathy is approximately 1–2 per 1,000 live births in developed countries[21], but just

over 500 cases were recorded in the registry over 3 years. Hayakawa and colleagues have, however, estimated that the incidence of moderate to severe neonatal encephalopathy in Japan is 0.37 per 1,000 live births[22]. Considering that 219 of 287 registered level II-III neonatal intensive care centres participated in the current registry (76.3%), our database is likely to have included the majority of eligible neonates. Nevertheless, caution is required to avoid drawing conclusions from studies based on case registries, which may be influenced by selection bias.

In conclusion, a national registry of TH in neonatal encephalopathy has been successfully established in Japan and maintained for 3 years. During this period, TH was applied and conducted in close concordance with the criteria and protocols used in previous large-scale RCTs. There was some improvement in practice, such as the time required for the initiation of TH. The mortality rate during the initial hospital stay was considerably lower than previous reports. International comparative studies may help identify factors associated with short-term outcome that would help investigators refine and improve the TH protocol.

Methods

This study was conducted in compliance with the Declaration of Helsinki. The protocols of the registry were approved by the Ethics Committees of Kurume University School of Medicine and Saitama Medical University, Japan. Since no patient identifiers were or are collected, the Ethics Committees advised that there is no statutory requirement for parental consent for data collection, and consent was not sought for the current registry.

The Neonatal Hypothermia Task Force Japan was formed by the Japan Society of Perinatal and Neonatal Medicine (JSPNM) and the Clinical Guidelines Committee for Neonatal Resuscitation in Japan (Neonatal Research Network Japan, Ministry of Health, Labour and Welfare [MHLW]) in June 2010 to implement evidence-based TH practice in Japanese neonatal intensive care centres. The Task Force launched an online case registry to monitor newborn TH practice in January 2012. The TH strategy was derived from the JSPNM and MHLW Japan Working Group Practice Guidelines Consensus Statement, which in turn had been developed by summarising and integrating the indications and cooling protocols used in large-scale RCTs[2–4]. All Japanese level II or III neonatal intensive care centres registered as designated hospitals for postgraduate clinical training with the Japanese Society for Neonatal Health and Development were invited to join the registry. Basic, mandatory clinical information for each case was input online via the official website of the Baby Cooling Registry of Japan. A unique identification number was allocated to each registered case. Data were anonymised so that patients could not be identified, obviating the need for individual consent for data collection. Although the registry guidance emphasised the importance of observing standard cooling protocols, participating units were requested to register all neonates (i) who underwent TH regardless of adherence to the guidance, and (ii) who were referred to the unit for consideration of TH but ultimately did not undergo cooling.

Case record forms were developed based on the format used in the UK TOBY Register[4], including patient characteristics, clinical condition at birth, severity of encephalopathy assessed by established scales[23,24], patterns of aEEG[25], core body temperature, cardiovascular and respiratory parameters, supportive treatments, use of sedatives and analgesics, clinical complications, and short-term outcomes at hospital discharge. Adverse events were reported in accordance with the guidance and protocol provided on the official website of the Baby Cooling Registry of Japan (Supplemental Table 2). Participating units were encouraged to obtain magnetic resonance images before discharge and perform developmental assessments at around 12 months and 2 years of age.

Statistical analysis. In this observational study, descriptive data analysis was performed for the dataset compiled during the first 3 years of the registry (between 1st January 2012 and 31st December 2014). For the current analysis, only data collected during the primary hospital stay were analysed. Each record was inspected for case duplication, apparent input errors or excessive unexplained missing data (>5% of the individual dataset without plausible explanations). To assess changes in patient characteristics and practice with time, data were grouped into 12-month periods according to the date of birth of each neonate, and the data from 2013 and 2014 were compared with those from 2012 using either the chi-squared test or Student's t-test with the Bonferroni correction. Values are shown as number (proportion, %) for categorical variables or mean ± standard deviation for normally distributed continuous variables.

References

1. Liu, L. *et al.* Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* **385,** 430–440, doi: 10.1016/s0140-6736(14)61698-6 (2015).
2. Gluckman, P. D. *et al.* Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* **365,** 663–670, doi: 10.1016/s0140-6736(05)17946-x (2005).
3. Shankaran, S. *et al.* Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *The New England journal of medicine* **353,** 1574–1584, doi: 10.1056/NEJMcps050929 (2005).
4. Azzopardi, D. V. *et al.* Moderate hypothermia to treat perinatal asphyxial encephalopathy. *The New England journal of medicine* **361,** 1349–1358, doi: 10.1056/NEJMoa0900854 (2009).
5. Simbruner, G., Mittal, R. A., Rohlmann, F. & Muche, R. Systemic hypothermia after neonatal encephalopathy: outcomes of neo.nEURO.network RCT. *Pediatrics* **126,** e771–778, doi: 10.1542/peds.2009-2441 (2010).
6. Jacobs, S. E. *et al.* Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial. *Archives of pediatrics & adolescent medicine* **165,** 692–700, doi: 10.1001/archpediatrics.2011.43 (2011).
7. Tagin, M. A., Woolcott, C. G., Vincer, M. J., Whyte, R. K. & Stinson, D. A. Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta-analysis. *Archives of pediatrics & adolescent medicine* **166,** 558–566, doi: 10.1001/archpediatrics.2011.1772 (2012).
8. Jacobs, S. E. *et al.* Cooling for newborns with hypoxic ischaemic encephalopathy. *The Cochrane database of systematic reviews* **1,** CD003311, doi: 10.1002/14651858.CD003311.pub3 (2013).
9. Perlman, J. M. *et al.* Part 11: Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation* **122,** S516–538, doi: 10.1161/circulationaha.110.971127 (2010).

10. Papile, L. A. *et al.* Hypothermia and neonatal encephalopathy. *Pediatrics* **133,** 1146–1150, doi: 10.1542/peds.2014-0899 (2014).
11. Austin, T., Shanmugalingam, S. & Clarke, P. To cool or not to cool? Hypothermia treatment outside trial criteria. *Archives of disease in childhood. Fetal and neonatal edition* **98,** F451–453, doi: 10.1136/archdischild-2012-302069 (2013).
12. Harris, M. N. *et al.* Perceptions and practices of therapeutic hypothermia in American neonatal intensive care units. *American journal of perinatology* **31,** 15–20, doi: 10.1055/s-0033-1334454 (2014).
13. Iwata, O. *et al.* Hypothermia for neonatal encephalopathy: Nationwide Survey of Clinical Practice in Japan as of August 2010. *Acta paediatrica* **101,** e197–202, doi: 10.1111/j.1651-2227.2011.02562.x (2012).
14. Iwata, O. *et al.* The baby cooling project of Japan to implement evidence-based neonatal cooling. *Therapeutic hypothermia and temperature management* **4,** 173–179, doi: 10.1089/ther.2014.0015 (2014).
15. Roka, A. & Azzopardi, D. Therapeutic hypothermia for neonatal hypoxic ischaemic encephalopathy. *Early human development* **86,** 361–367, doi: 10.1016/j.earlhumdev.2010.05.013 (2010).
16. Edwards, A. D. *et al.* Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. *Bmj* **340,** c363, doi: 10.1136/bmj.c363 (2010).
17. Shankaran, S. *et al.* Effect of depth and duration of cooling on deaths in the NICU among neonates with hypoxic ischemic encephalopathy: a randomized clinical trial. *Jama* **312,** 2629–2639, doi: 10.1001/jama.2014.16058 (2014).
18. Azzopardi, D. *et al.* Implementation and conduct of therapeutic hypothermia for perinatal asphyxial encephalopathy in the UK–analysis of national data. *PloS one* **7,** e38504, doi: 10.1371/journal.pone.0038504 (2012).
19. Pfister, R. H. *et al.* The Vermont Oxford Neonatal Encephalopathy Registry: rationale, methods, and initial results. *BMC pediatrics* **12,** 84, doi: 10.1186/1471-2431-12-84 (2012).
20. Kracer, B., Hintz, S. R., Van Meurs, K. P. & Lee, H. C. Hypothermia therapy for neonatal hypoxic ischemic encephalopathy in the state of California. *The Journal of pediatrics* **165,** 267–273, doi: 10.1016/j.jpeds.2014.04.052 (2014).
21. Lee, A. C. *et al.* Intrapartum-related neonatal encephalopathy incidence and impairment at regional and global levels for 2010 with trends from 1990. *Pediatric research* **74** Suppl 1, 50–72, doi: 10.1038/pr.2013.206 (2013).
22. Hayakawa, M. *et al.* Incidence and prediction of outcome in hypoxic-ischemic encephalopathy in Japan. *Pediatrics international: official journal of the Japan Pediatric Society* **56,** 215–221, doi: 10.1111/ped.12233 (2014).
23. Sarnat, H. B. & Sarnat, M. S. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. *Archives of neurology* **33,** 696–705 (1976).
24. Thompson, C. M. *et al.* The value of a scoring system for hypoxic ischaemic encephalopathy in predicting neurodevelopmental outcome. *Acta paediatrica* **86,** 757–761 (1997).
25. Thoresen, M., Hellstrom-Westas, L., Liu, X. & de Vries, L. S. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. *Pediatrics* **126,** e131–139, doi: 10.1542/peds.2009-2938 (2010).

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K.T., S.I., and O.I. designed the study and the survey items. K.T., T.M., J.S., T.T., T.I., S.H., N.Y., A. Takahashi, A. Takeuchi, and T.T. participated in the data collection. K.T., T.M., S.I., Y.A., and O.I. performed the statistical analyses. K.T., S.I., T.T., Y.A., H.S., M.T., S.H., M.N., and O.I. contributed to the interpretation of the results. K.T., S.I., and O.I. drafted the manuscript, which was critically reviewed and revised by T.M., T.T., H.S., M.T., S.H., and M.N. All authors have seen and approved the final version of this manuscript.

Additional Information

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