The Baby Cooling Project of Japan to Implement Evidence-Based Neonatal Cooling

Osuke Iwata,^{1,2} Toshiki Takenouchi,³ Sachiko Iwata,¹ Makoto Nabetani,⁴ Takeo Mukai,⁴ Jun Shibasaki,⁵ Kennosuke Tsuda,¹ Takuya Tokuhisa,⁶ Hisanori Sobajima,⁷ and Masanori Tamura⁷

Therapeutic hypothermia was first recommended as a standard of care by international guidelines in 2010. However, at that time, the number of centers capable of providing standard cooling was limited even in Japan. The aim of this project was to implement a nationwide network of evidence-based cooling within 3 years. A taskforce was formed in June 2010 to undergo the primary nationwide practice survey, design of action plans, and the appraisal of interventions by involving all registered level-II/III neonatal intensive care units in Japan. Based on findings from the primary survey, aggressive action plans were introduced that focused on the formulation of clinical recommendations, facilitation of educational events, and opening of an online case registry. Findings from the follow-up survey (January 2013) were compared with the results from the primary survey (June 2010). Four workshops and three consensus meetings were held to formulate clinical recommendations, which were followed by the publication of practical textbooks, large-scale education seminars, and implementation of a case registry. A follow-up survey covering 253 units (response rate: 89.1%) showed that cooling centers increased from 89 to 135. Twelve prefectures had no cooling centers in 2010, whereas all 47 prefectures had at least one in 2013. In cooling centers, adherence to the standard cooling protocols and the use of servo-controlled cooling devices improved from 20.7% to 94.7% and from 79.8% to 98.5%, respectively. A rapid improvement in the national provision of evidence-based cooling was achieved. International consensus guidelines coupled with domestic interventions might be effective in changing empirical approaches to evidence-based practice.

Introduction

A SERIES OF LARGE-SCALE randomized-controlled trials (RCTs) of therapeutic hypothermia (TH) consistently demonstrated the neuroprotective effect of cooling in asphyxiated newborn infants (Gluckman *et al.*, 2005; Shankaran *et al.*, 2005; Azzopardi *et al.*, 2009; Jacobs *et al.*, 2013). Follow-up studies of three RCTs suggested some benefit of TH even at early school age (Guillet *et al.*, 2012; Shankaran *et al.*, 2012; Azzopardi *et al.*, 2014). TH was recommended as a standard of care for moderate to severe neonatal encephalopathy for the first time in the Consensus Statement and Treatment Recommendation on Cardio-Pulmonary Resuscitation revised in October 2010 (2010 CoSTR) (Perlman *et al.*, 2010). Recent studies have addressed the potential

benefit of cooling applied at different times, duration, and depth, or to additional groups of newborn infants (Shankaran, 2012). These were speculated to improve the neuroprotective effect of cooling and to increase the range of infants who would benefit. Simple, alternative cooling modalities have been investigated for use in low-resource settings, such as in developing countries (Robertson *et al.*, 2008; Iwata *et al.*, 2009; Thayyil *et al.*, 2009), and during transportation (Kendall *et al.*, 2010). However, thus far, abbreviated cooling strategies applied in low-resource settings have mainly been linked with trends toward increased unfavorable events (Robertson *et al.*, 2008; Thayyil *et al.*, 2009), suggesting that, in clinical practice, protocols used in large-scale RCTs are currently the only strategies which assure beneficial effects of TH.

¹Department of Pediatrics & Child Health, Centre for Developmental & Cognitive Neuroscience, Kurume University School of Medicine, Fukuoka, Japan.

²St. Mary's Hospital, Fukuoka, Japan.

³Division of Pediatric Neurology, Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan.

⁴Division of Pediatrics, Yodogawa Christian's Hospital, Osaka, Japan.

⁵Division of Neonatology, Kanagawa Children's Medical Center, Kanagawa, Japan.

⁶Division of Neonatology, Kagoshima City Hospital, Kagoshima, Japan.

⁷Department of Pediatrics, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan.

This project aimed at implementing evidence-based cooling protocols and at developing a nationwide network of TH for neonatal encephalopathy in Japan within 3 years.

Materials and Methods

The protocols of the surveys and the registry were approved by the Ethics Committees of Kurume University School of Medicine and Saitama Medical University.

Foundation of a taskforce, initial survey, and action plans

In June 2010, the Japan Society of Perinatal and Neonatal Medicine, and the Clinical Guidelines Committee for Neonatal Resuscitation in Japan (Neonatal Research Network Japan, Ministry of Health, Labour and Welfare), formed a taskforce (Neonatal Hypothermia Task Force Japan) with four pediatricians (Osuke Iwata, Toshiki Takenouchi, Makoto Nabetani, and Masanori Tamura; Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/ther). To capture the distribution of neonatal intensive care units that were able to provide standard TH at the time, the taskforce conducted a nationwide survey in August 2010 (Survey 2010), which consisted of 45 questions asking the size and type of the unit, locally available resources, therapeutic strategy for neonatal encephalopathy, cooling protocol, supportive treatments, and follow-up programs (Iwata *et al.*, 2012). This survey showed a significant shortage in the number of units that were capable of providing TH, as well as poor adherence to the standard TH protocol. This result

forced the taskforce to form aggressive interventions, which comprised (i) formulation of clinical recommendations, (ii) implementation of evidence-based TH for clinicians, and (iii) facilitation of an online case registry (Fig. 1).

Formulation of domestic clinical recommendations

Four large-scale workshops were scheduled between November 2010 and July 2011 in conjunction with major domestic scientific meetings in perinatal medicine. The workshops aimed at (i) introducing the concept of revised international recommendations for neonatal resuscitation and TH (Perlman *et al.*, 2010), (ii) sharing the domestic issues in Japan highlighted from the Survey 2010 (Iwata *et al.*, 2012), (iii) presenting a draft of clinical recommendations of TH (drafted by the taskforce members by summarizing the entry criteria and protocols for large-scale RCTs), and (iv) calling for public and expert opinion. Three consensus meetings were held to form an expert committee (Supplementary Table S1). Domestic experts of neonatal intensive care, child neurology, and clinical investigations were invited from members of the council board of domestic medical societies in pediatrics and perinatal medicine. The committee discussed the public and expert comments obtained at or after the workshops. The committee also delineated specific domestic backgrounds in Japan, which may require consideration in applying clinical recommendations in Western countries. The draft of the clinical recommendations was revised by the committee members and was presented for approval at the workshop in July 2011.

FIG. 1. Timeline of action plans by the Neonatal Hypothermia Task Force Japan. The Neonatal Hypothermia Task Force was created in June 2010 to implement evidence-based cooling in newborn infants in Japan. Action plans included formulation of clinical recommendations based on a series of workshops and consensus meetings, facilitating education seminars, dissemination of practical textbooks and opening of an online case registry for cooled infants. Two separate surveys were conducted before and after these intensive interventions. Most workshops, consensus meetings and educational seminars were held in conjunction with annual meetings for the Japan Society for Premature and Newborn Medicine (November 2010, Kobe; November 2011, Tokyo; November 2012, Kumamoto), Convention for Japanese Perinatal Centers (January 2011, Osaka), the Neonatal Respiratory Care and Monitoring Forum (February 2011 and 2012, Omachi), and the Japan Society of Perinatal and Neonatal Medicine (July 2011, Sapporo; July 2012, Saitama). A principal investigator of the UK TOBY Trial and the leading author of the chapter for neonatal resuscitation, 2010 CoSTR, were invited to three of these events as discussants. CoSTR, Consensus on Resuscitation Science and Treatment Recommendations.

Educational interventions

Three educational seminars were scheduled in conjunction with major scientific meetings in perinatal medicine. These seminars targeted a wide range of medical staffs who were unfamiliar with TH for newborn infants. The taskforce also published a practical textbook of TH, which illustrated the basic principles and procedures of TH with maximum emphasis on the relevance and importance of observing the standard cooling protocols (Tamura *et al.*, 2010). Another practical textbook of neonatal resuscitation was published to improve the quality of neonatal resuscitation and the triage of infants who may have a clinical indication for TH (Tamura, 2010).

Case registry

To persistently monitor the practice of TH in newborns, an online case registry was developed. While basic survey items, such as patients' clinical background variables, severity of encephalopathy, core body temperatures, supportive treatments, adverse events, and short-term outcomes, were adopted from the UK TOBY Register (Azzopardi *et al.*, 2012), additional items, such as the type of sedation and other neuroprotective treatments, were given to highlight domestic characteristics in Japan (Neonatal Hypothermia Task Force Japan, 2012). All of the level-II/III neonatal intensive care centers were invited to join the registry by applying for an online institutional account, with which clinical information can be submitted via the official website of the Baby Cooling Japan Registry (Neonatal Hypothermia Task Force Japan, 2012). Representatives of registered centers reported primary and secondary information within 2 months after admission and discharge of the cooled infant, respectively. We plan to convey the findings from the registry on the website of the case registry (Neonatal Hypothermia Task Force Japan, 2012) and at twice-yearly educational seminars of TH.

Assessment

To assess changes in clinical practice before and after the implementation of the program, a secondary survey was conducted in January 2013 (Survey 2013) by sending a set of questionnaires on January 1 to all 284 level-II/III neonatal intensive care units registered with the Japan Society of Perinatal and Neonatal Medicine (January, 2013). Five questionnaires about the type/size of the unit and the application of TH (addressed to all centers) and 19 extensive questionnaires about the cooling indication/protocol, adverse events, supportive treatments, and follow-up protocols (addressed to cooling centers only) were extracted from the items of the Survey 2010 (Supplementary Table S2) (Iwata *et al.*, 2012). A reminder letter was sent on 28th January to nonresponding centers by extending the deadline from 31st January to 7th February. Results from the initial and follow-up surveys were compared using the chi-square test or Fisher's exact test.

Results

Formulation of domestic clinical recommendations

At the workshops, the critical gaps in practice of TH between Japan and Western countries, which were highlighted by the Survey 2010, were shared, resulting in the approval of the general concept of implementing the protocols of TH

used in large-scale RCTs by the audience. Public/expert opinions on the draft of clinical recommendations were mainly requests to approve empirically developed/disseminated domestic cooling protocols, which had different indication criteria (e.g., 5-minute Apgar scores ≤ 6), core-body temperature monitoring (e.g., nasopharyngeal), depths (e.g., 35°C), durations (e.g., 98 hours), modalities (e.g., ice bags), and supportive treatments (e.g., routine use of muscle relaxants) (Iwata and Takenouchi, 2012; Iwata *et al.*, 2012). The expert committee carefully discussed the relevance of such modifications of the standard protocols. However, no clinical evidence was found to support the equality/superiority of the modified protocols. The committee concluded that the difference in variables induced by any of these changes might alter the beneficial effect of TH, and that the clinical protocols of large-scale RCTs should be adopted without changes. The final version of the clinical recommendations was approved by the attendees of the final workshop in July 2011, and this was then published in Japanese and English (Takenouchi *et al.*, 2012).

Educational interventions

Practical textbooks of neonatal resuscitation and TH were published in January and April 2011, respectively (Tamura, 2010; Tamura *et al.*, 2010). Three large-scale education seminars were held between November 2011 and November 2012 with attendance from 256 institutions. Further education seminars are scheduled approximately twice a year.

Case registry

The benefit and feasibility of opening an online case registry for neonatal TH were strongly supported by attendees of the workshops and consensus meetings. In January 2012, an online case registry for neonatal hypothermia was opened by initially involving 73 neonatal intensive care centers across the nation (Neonatal Hypothermia Task Force Japan, 2012). By the end of October 2013, the number of participating centers reached 145, resulting in 325 cumulative cases registered (Fig. 2). Findings of this registry will be reported elsewhere.

Changes in practice in 3 years

The Survey 2013 obtained responses from 253 level-II/III neonatal intensive care units, yielding a response rate of 89.1% (slightly higher than 83.9% in the Survey 2010). The number of cooling centers increased from 89 in the Survey 2010 (Iwata *et al.*, 2012) (55 level-II and 34 level-III units) to 135 in the Survey 2013 (70 level-II and 65 level-III units; $p < 0.05$). In 2010, 12 of 47 prefectures had no cooling centers. However, in 2013, TH was readily available in all 47 prefectures (Table 1).

In the Survey 2013, even in the centers that had not applied TH at the time, 11 units were ready to provide TH and three units were preparing to provide TH in the near future. With regard to the reasons for "not cooling," a lack of human/medical resources and clinical evidence decreased from 85.1% to 75.0% and from 18.4% to 2.6%, respectively. However, a lack of cases and/or the presence of neighboring cooling centers increased from 21.1% to 41.2%. In active cooling centers, adherence to the standard cooling protocols

FIG. 2. Number of registrations and centers which registered cases. Monthly and cumulative numbers of (A) registered patients to the Baby Cooling Japan Registry and (B) neonatal intensive care centers which registered patients, showing consistent number of registrations and participating centers since the opening of the system in January 2012.

and the use of servo-controlled cooling devices significantly improved from 20.7% to 94.7% ($p < 0.001$) and from 79.8% to 98.5% ($p < 0.001$), respectively. The use of selective head cooling and whole body cooling changed from 88.8% to 56.1% and from 11.2% to 43.9%, respectively. A total of 91.8% and 92.2% of cooled infants were followed up at least until the age of 6 years in 2010 and 2013, respectively.

Discussion

To promote evidence-based TH for neonatal encephalopathy, a series of aggressive educational events were delivered on a nationwide level since the publication of 2010 CoSTR. The program focused on the formulation of domestic clinical recommendations, education of medical staff, and facilitation of a national case registry. Subsequently, national provisions of standard TH were achieved within 3 years. Our findings suggest that the approval of new therapeutic options by international guidelines may benefit from simultaneous educational action plans at the domestic level.

The neuroprotective effect of TH has been established in encephalopathic newborn infants (Gluckman *et al.*, 2005; Azzopardi *et al.*, 2009; Shankaran *et al.*, 2005). However, to assure the benefit of this treatment, standard cooling criteria and protocols should be observed until further clinical evidence confirms the advantage of newly developed regimens (Kendall *et al.*, 2010; Thoresen, 2010). As shown by the Survey 2010 (Iwata *et al.*, 2012), preparations for TH were

unsatisfactory even in Japan. Strong trends toward empirically modified protocols for indication and temperature control were evident at the time, presumably because of a specific background in Japan that TH had clinically been applied in some neonatal intensive care units using empirically acquired protocols since the late 1990s (Iwata and Takenouchi, 2012). This urged the taskforce to perform prompt and efficient intervention to implement standard cooling protocols across the nation. An intensive program was designed to enlighten the relevance and importance of adhering to an evidence-based protocol by facilitating a series of educational events. This program targeted a wide range of clinical staff, including midwives, obstetricians, pediatricians, neonatologists, and nurses. The Survey 2013 showed that, apart from the increase in the number of cooling units, adherence to standard cooling protocols significantly improved. Even in units that still did not provide TH, the reasons for “not cooling” shifted from a lack of evidence and human/medical resources to a lack of cases and the presence of nearby cooling centers. Such dramatic changes might have accelerated approval of TH for asphyxiated newborn infants by the national health insurance agency in April 2012.

When a new therapeutic strategy is being introduced to clinical practice, priority should be placed on assurance of the safety of the treatment (Laventhal *et al.*, 2012). However, in reality, therapies are often applied preliminarily before the accumulation of clinical evidence, where techniques are acquired using empirical approaches (Iwata and Takenouchi, 2012).

TABLE 1. CHANGE IN PRACTICE AT NEONATAL INTENSIVE CARE CENTERS THAT PROVIDED THERAPEUTIC HYPOTHERMIA IN AUGUST 2010 AND JANUARY 2013

	2010 (n = 89)	2013 (n = 135)	p-Values ^a
Cooled infants in previous 12 months	234	313	Not tested
Cooling indication			
Same with large-scale RCTs	18 (20.7)	125 (94.7)	<0.001
Other criteria	69 (79.3)	7 (5.3)	
Cooling modality			
Whole body	10 (11.2)	58 (43.9)	<0.001
Selective head	79 (88.8)	74 (56.1)	
Cooling device used			
Purpose-built ^b	71 (79.8)	129 (98.5)	<0.001
Alternative	18 (20.2)	2 (1.5)	
Continuous body temperature monitoring			
Yes	73 (84.9)	126 (95.5)	0.026
No	13 (15.1)	6 (4.5)	
Monitoring of rectal or esophageal temperature			
Yes	73 (82.0)	120 (88.9)	0.346
No	16 (18.0)	15 (11.1)	
Target body core temperature			
Same with RCTs ^c	7 (7.9)	41 (30.4)	<0.001
Difference $\leq 0.5^{\circ}\text{C}$	70 (13.5)	91 (2.2)	
Difference $> 0.5^{\circ}\text{C}$	12 (13.5)	3 (2.2)	
Use of aEEG			
Yes	15 (16.9)	89 (67.4)	<0.001
No	74 (83.1)	43 (32.6)	
Neuroimaging studies performed routinely			
MRI	81 (91.0)	131 (97.0)	0.147
CT scan	33 (37.1)	23 (17.0)	0.003
Cooling duration			
72 hours	63 (76.8)	126 (95.5)	<0.001
Other durations	19 (23.2)	6 (4.5)	
Rate of rewarming			
$\leq 0.5^{\circ}\text{C}/\text{hour}$	20 (23.0)	96 (73.3)	<0.001
$\leq 1^{\circ}\text{C}/\text{day}$ or slower	67 (77.0)	35 (26.7)	
Routine use of muscle relaxant			
Yes	16 (19.0)	5 (3.8)	0.001
No	68 (81.0)	127 (96.2)	
Minimum follow-up duration of infants			
Up to 3 years	58 (67.4)	84 (65.6)	0.940
3–6 years	21 (24.4)	34 (26.6)	
Longer than 6 years	7 (8.1)	10 (7.8)	
Assessment of neurodevelopmental outcome using individualized batteries			
Available	71 (88.8)	114 (84.4)	0.679
Not available	9 (11.3)	21 (15.6)	

Values are shown as number (%), unless otherwise stated.

^aChi-square test or Fisher's exact test between 2010 and 2013.

^bElectronic, servo-controlled cooling devices approved by the Japanese Ministry of Health, Labour, and Welfare for the purpose of therapeutic hypothermia.

^c34.5 (selective head cooling) or 33.5 (whole body cooling) -0.5°C .

aEEG, amplitude-integrated EEG; RCT, randomized-controlled trial.

Recently, a group of five regional centers reported improved quality of TH using standard quality control methodology, which addressed timely identification and referral of newborn infants to cooling centers, implementation of standard cooling and monitoring protocols, assessment of the clinical condition and outcome using biomarkers and standardized neurodevelopmental follow up, and enrolment of infants in a national registry (Olsen *et al.*, 2013). These findings, along with our experience, highlight the importance

of a systematic approach for improving the quality of practice using persistent education and sustained multidisciplinary leadership.

In our current project, we conducted a set of surveys involving most registered level-II/III neonatal intensive care centers in Japan, which demonstrated significant changes in practice before and after our interventions. However, we were unable to evaluate the direct impact of our program, because it targeted the entire nation. Therefore, the drastic

change in practice observed in more than 200 level-II/III centers might, at least in part, be due to other factors, such as the publication of systematic reviews and 2010 CoSTR itself (Edwards *et al.*, 2010; Perlman *et al.*, 2010; Jacobs *et al.*, 2013).

Several other factors, which are specific to the system of neonatal medicine in Japan, may have to be highlighted before translating our findings into clinical practice in other parts of the world. Neonatal intensive care centers in Japan are generally small with less than 15 intensive cots. Most of these provide tertiary care with a relatively small number of staff (Kusuda *et al.*, 2006), where clinical protocols are more likely to be abbreviated. However, empirical modification of standard therapy also occurs in other developed countries (Azzopardi *et al.*, 2012; Olsen *et al.*, 2013). Careful and persistent assessments are required to compare practice in different countries. This could be achieved by comparing adherence to the standard protocol between registries conducted in another country (e.g., the United Kingdom) and Japan.

Conclusions

We observed a rapid and drastic improvement in adherence to standard cooling protocols following the update of international guidelines on resuscitation and the integration of nationwide implementation programs in Japan. International consensus guidelines coupled with domestic strategic action plans, including the formulation of clinical recommendations, training of medical staff, and facilitation of a national case registry, might be effective in changing empirical approaches to evidence-based medical practice. Sustained educational programs, intermittent assessment of practice, and facilitation of a long-term follow-up system with appropriate assessment tools of neurodevelopmental outcomes are required.

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Disclosure Statement

The authors declare no conflicts of interest.

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Address correspondence to:

Osuke Iwata, MD, PhD

Department of Pediatrics & Child Health

Centre for Developmental & Cognitive Neuroscience

Kurume University School of Medicine

67 Asahimachi

Kurume

Fukuoka 830-0011

Japan

E-mail: o.iwata@ucl.ac.uk