Institution: University of Bristol

Unit of Assessment: 4 – Psychology, Psychiatry and Neuroscience

Title of case study: Therapeutic hypothermia saves thousands of babies each year across the developed world from severe disability or death

1. Summary of the impact

Since 2010, infants around the world have been saved from death or severe disability as a result of research conducted by Professor Marianne Thoresen and her team at the University of Bristol. Translational research conducted between 1998 and 2010 by the Thoresen group showed that mild cooling of newborn children who had suffered a lack of oxygen during labour and delivery reduced death and disability by over 50%. Extensive publication on this treatment and practical training for neonatal staff, led by the Bristol team since 2008, has transformed the management of neonatal brain injury. By 2010/11, therapeutic cooling had been adopted as standard treatment throughout the developed world, saving thousands of children from death or severe disability, including cerebral palsy and epilepsy. Therapeutic hypothermia also saves the NHS and UK families about £200 million/year in care and compensation costs.

2. Underpinning research

Between one and two babies for every thousand born at term suffer a lack of oxygen during labour and delivery that is severe enough to injure the brain (hypoxic-ischaemic encephalopathy (HIE)). Over the past few decades, improvements in the resuscitation of asphyxiated newborn infants have greatly increased the chances of their survival. However, until very recently, no intervention had been demonstrated to reduce brain injury and subsequent disability. In January 1998, Marianne Thoresen, Senior Lecturer (now Professor) in Neonatal Neuroscience, and Andrew Whitelaw, Professor of Neonatal Medicine, established a laboratory and clinical research programme at the University of Bristol to investigate and develop therapeutic hypothermia as a treatment for neonatal HIE.

Optimising the therapeutic efficacy of hypothermia

Previous studies into the neuroprotective effects of hypothermia had variable results, with some showing no neuroprotective effect at all. In 2003, using a piglet model of total-body hypoxia-ischaemia, Thoresen showed that selective head cooling by only a few degrees, combined with mild systemic hypothermia, substantially reduced brain injury but, crucially, that the treatment was not effective unless the animals were sedated/anaesthetised [1]. In 2008, Thoresen and her colleagues published results that showed that the neuroprotective efficacy of hypothermia treatment fell dramatically if cooling was delayed [2]. Importantly, the research group also demonstrated that mild cooling (in the absence of hypoxia) did not injure the brain, even when assessment included the use of sensitive molecular markers for neuronal injury.

Importance of cardiovascular monitoring

With the involvement of both of the neonatal intensive care units in Bristol, the Thoresen group conducted a clinical feasibility study and systematically documented cardiovascular changes associated with therapeutic cooling and rewarming [3]. They were the first researchers to point out that cardiovascular instability can occur with therapeutic hypothermia and this knowledge was

critical in setting up a process of careful monitoring and correction that could be used to avoid adverse effects in clinical trials.

CoolCap and TOBY: multi-centre randomised clinical trials

The first multi-centre randomised trial of the clinical feasibility study [3] for CoolCap [4], was led by Bristol and conducted between 1999 and 2002. This study showed the treatment to be safe, with improved outcome in infants without the most severe baseline electroencephalographic changes. It subsequently led to TOBY [5], the largest multi-centre trial of total body cooling for HIE, conducted between 2002 and 2006, in which Bristol was again a lead centre. The findings of this trial confirmed the brain protection afforded by cooling and were reported in the *New England Journal of Medicine* in 2009 [5].

Bristol contributions

In conducting this research, the Bristol team has collaborated with colleagues in a number of other universities including Aukland, Oslo, Gothenburg, UCL, Imperial and INSERM (Paris). The Bristol team carried out the critical research on piglet models. This underpinned clinical trials, in which Bristol played a leading role. Bristol has also led in the analysis of the clinical data and in the dissemination of information through peer-reviewed publication and practical training of neonatal staff in the treatment methodologies. This research was carried out between 1998 and 2010 by:

- Marianne Thoresen: Senior Lecturer 1998-2001; Reader 2001-2003; Professor of Neonatal Neuroscience 2004-2014
- Andrew Whitelaw: Professor of Neonatal Medicine 1998-2011
- Saulius Satas: Research Fellow 1998-2002
- James Tooley: Research Fellow 2001-2005
- Helen Porter: Senior Lecturer in Perinatal Pathology 1998-2001

3. References to the research

[1] Tooley, J.R., Satas, S., Porter, H., Silver, I.A. & Thoresen, M. (2003) 'Head cooling with mild systemic hypothermia in anesthetized piglets is neuroprotective', *Annals of Neurology*, 53:65-72. DOI: 10.1002/ana.10402

[2] Karlsson, M., Tooley, J.R., Satas, S., Hobbs, C.E., Chakkarapani, E., Stone, J., Porter, H. & Thoresen, M. (2008) 'Delayed hypothermia as selective head cooling or whole body cooling does not protect brain or body in newborn pig subjected to hypoxia-ischemia', *Pediatric Research*, 64:74-8. DOI: 10.1203/PDR.0b013e318174efdd

[3] Thoresen, M. & Whitelaw, A. (2000) 'Cardiovascular changes during mild therapeutic hypothermia and rewarming in infants with hypoxic-ischemic encephalopathy', *Pediatrics,* 106: 92-9. Can be supplied upon request.

[4] Gluckman, P.D., Wyatt, J.S., Azzopardi, D., Ballard, R., Edwards, A.D., Ferriero, D.M., Polin, R.A., Robertson, C.M., Thoresen, M., Whitelaw, A. & Gunn, A.J. (2005) 'Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial', *Lancet*, 365:663-70. DOI: 10.1016/S0140-6736(05)17946-X

[5] Azzopardi, D.V., Strohm, B., Edwards, A.D., Dyet, L., Halliday, H.L., Juszczak, E., Kapellou, O., Levene, M., Marlow, N., Porter, E., Thoresen, M., Whitelaw, A. & Brocklehurst, P. (2009) 'Moderate hypothermia to treat perinatal asphyxial encephalopathy', *New England Journal of Medicine*,361:1349-58. DOI: 10.1056/NEJMoa0900854

[6] Thoresen, M., Hellström-Westas, L., Liu, X. & de Vries, L.S. (2010) 'Effect of hypothermia on amplitude-integrated electroencephalogram in infants', *Pediatrics*,126:e131-9. DOI: 10.1542/peds.2009-2938

4. Details of the impact

An estimated 1 to 4 births/1000 in the UK results in HIE (i.e. approximately 1625 of the 650,000 births/year). Before the introduction of therapeutic hypothermia, a quarter of affected newborn babies were likely to die, while the 75% that survived were at risk of severe handicap. Other impacts include lower cognitive scores and poorer scholastic achievement; these children often require additional educational support. This medical, emotional and financial impact places a major burden on the individuals affected, their families and society as a whole.

Saving infants from death or disability: improved patient outcomes

In 2010, Thoresen and Whitelaw co-authored a meta-analysis of clinical studies of moderate cooling for prevention of HIE in newborn babies. The meta-analysis included the two largest, Bristol-led, trials (see above) and confirmed the substantial benefits of hypothermia in HIE [a]. The meta-analysis showed that at 18 months of age after having received therapeutic hypothermia, there was:

- a significant reduction in mortality,
- increased survival with normal neurological function,
- and reduced disability (including cerebral palsy).

Since 2011, therapeutic hypothermia has been provided by tertiary neonatal intensive care units in all regions of the UK. In the UK, approximately 400 children are saved annually from disability or death (the published trial data and audit of the Bristol results indicate improved outcome in 20-30% of those treated) and as the treatment is now used across the developed world, the global estimate of children saved annually is several thousand.

Impacting UK and international treatment guidelines

In May 2010, the UK's National Institute of Clinical Excellence (NICE) issued new guidance stating that there was sufficient evidence on the safety and efficacy of therapeutic hypothermia "to support the use of this procedure in carefully selected neonates..."([b], which refers to meta-analysis by Thoresen and her colleagues [a]). The guidance is supported by an overview of the research compiled by NICE including the opinions of Specialist Advisers, including Thoresen and Whitelaw [c, cites 3,4].

In July 2010, the British Association of Perinatal Medicine published a position statement recommending that "babies presenting with moderate to severe neonatal encephalopathy within the first few hours after delivery should undergo therapeutic cooling" [d, cites 4, 5 & a].

That same year, the International Liaison Committee on Resuscitation (ILCOR) produced the 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science. One of the major new recommendations in the 2010 consensus was that "Therapeutic hypothermia should be considered for infants born at term or near-term" with "moderate to severe hypoxic-ischemic encephalopathy" [e, cites 4, 5 & a].

Training of neonatal medical and nursing staff

Thoresen and Whitelaw have been running courses on therapeutic hypothermia for neonatal medical and nursing staff since 2008 in the UK and abroad – 12 to date in UK, with an average of 40 applicants/course, and courses in San Francisco (2007) Tampa (Florida) 2008, Vienna (2008) Tel Aviv (2009), Kuwait (2008), Lisbon (2009) Amsterdam (2010) and Orlando (2011). The courses are

practical, interactive and hands-on, recognising the critical importance of practical skills as well as knowledge in using cooling safely and effectively.

Saving resources

An independent analysis of the cost effectiveness of therapeutic hypothermia showed that within the first 18 months after birth, the mean health service cost was £22,324 in the cooled group versus £18,537 in the noncooled group, but that these increased costs offered "good value for money" due to the effectiveness of the procedure in reducing mortality and severe disability [f].

The average compensation award made in cases of cerebral palsy after perinatal asphyxia in the UK is £3 million if negligence is proven. This is reckoned to be the life-time cost of care and lost earnings for cerebral palsy. Thus one can conclude that the introduction of therapeutic hypothermia is saving the UK (NHS and families) about £200 million annually.

5. Sources to corroborate the impact

[a] A meta-analysis of clinical studies providing unequivocal evidence of the benefits of therapeutic hypothermia in HIE: Edwards, A.D., *et al.,* (2010) '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.

[b] New guidelines for using therapeutic hypothermia in the treatment of HIE issued by NICE in response to the meta-analysis results [a].The National Institute of Clinical Excellence (NICE) (May 2010) 'Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury', *Interventional procedure guidance 347*. < http://www.nice.org.uk/nicemedia/live/11315/48809/48809.pdf>

[c] Provides overview of the evidence used to develop guidelines [b], in which [3 & 4] are cited: NICE (April 2008) 'Interventional procedure overview of therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury', *Interventional Procedures Programme*, IP 552 <http://www.nice.org.uk/nicemedia/live/11315/41111/41111.pdf> [cites 3,4].

[d] Evidence that research was directly used to develop position statement by BAPM: British Association of Perinatal Medicine (July 2010) *Position Statement on Therapeutic Cooling for Neonatal Encephalopathy*, London: BAPM. <http://www.bapm.org/publications/documents/guidelines/Position_Statement_Therapeutic_Cooling_Neonatal_Encephalopathy_July%202010.pdf> [cites 4, 5 & a].

[e] Evidence that research was directly used to inform and develop an international consensus and recommendation for treatment in neonatal resuscitation: Perlman, J.M. *et al.* (2010) '2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations, Part 11: Neonatal Resuscitation', *Circulation,* 122(16 Suppl 2):S516-S538.DOI: 10.1161/CIRCULATIONAHA.110.971127 [cites 4, 5 & a]

[f] Gives cost-benefit estimates of therapeutic hypothermia treatment, showing the treatment is cost-effective: Regier, D.A. *et al.* (2010) 'Cost-effectiveness of therapeutic hypothermia to treat neonatal encephalopathy', *Value in Health,* 13 (6):695-702. DOI: 10.1111/j.1524-4733.2010.00731.x