Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Moderate hypothermia as a therapy for neonatal encephalopathy improves survival and reduces disability

1. Summary of the impact

Our early work on large animal models underpinned trials undertaken by ourselves and by others, which in turn have resulted in therapeutic hypothermia becoming standard care for infants with moderate to severe neonatal encephalopathy. In 2010 this was recommended in NICE guidance. Over 3,000 babies have now been given this treatment, and we estimate that 450 have avoided death or serious neurological disability. The estimated economic value of this is over £125 million.

2. Underpinning research

Problems around the time of birth causing a lack of oxygen to the fetus (birth asphyxia) can lead to disordered brain function called neonatal encephalopathy which can result in death, long-term brain damage, cerebral palsy, epilepsy and other significant cognitive, developmental and behavioural problems. Neonatal encephalopathy occurs in 750-1,125 infants in the UK every year. The financial and human costs to infants affected, their parents, professionals and wider society are enormous.

Extensive experimental and clinical research has been carried out at UCL since the early 1980s into the evolution and timing of energy failure and cell death following perinatal hypoxia-ischaemia. Osmond Reynolds and his team of researchers at UCL were struck by the group's magnetic resonance spectroscopy data showing that the infant's brain is normal in the hours after asphyxia and cell death occurs only after a distinct delay of several hours. Delayed brain injury (called "secondary energy failure" by Reynolds) was a critical new idea: this secondary deterioration in brain energy metabolism was observed in both babies with neonatal encephalopathy and then in animal models **[1]**. This delay in cell death opened the possibility of therapeutic intervention in what had previously been considered an impossible situation. A key breakthrough came in 1995 when the UCL team demonstrated that if whole-body cooling was introduced in the period just after hypoxia-ischaemia in the piglet brain, secondary energy failure was ameliorated or prevented and brain cell death reduced **[2]**.

Confirmatory studies in Sweden and New Zealand built on these demonstrations, and as a result, the first clinical trial of therapeutic hypothermia was initiated. This was the multicentre CoolCap Trial, which involved selective head cooling. John Wyatt (UCL) and Peter Gluckman (Auckland) were the principal investigators of this trial. The first patient was enrolled in 1999 and the study was published in the Lancet in 2005 **[3]**. The trial used selective head cooling and mild body cooling (to 34.5^{o}C) to minimise potential side effects of cooling. The results were encouraging; although Coolcap showed a non-significant trend to improvement with cooling in the primary outcome of death or disability at 18 months overall, there was a clear and significant benefit when infants with very severe or long-established injury were excluded.

Other major studies of cooling followed, building on our early work. As we had demonstrated that there had been no major adverse effects of controlled cooling to 34.5^{o}C and whole body cooling seemed more practical, most of the subsequent cooling studies used whole body cooling to a core temperature of 33.5^{o}C. The next major cooling study to be published was that run by the National Institute for Child Health and Human Development (NICHD), which showed a significant effect of cooling. In the UK, total body hypothermia for neonatal encephalopathy (TOBY) trial was set up. This trial was still recruiting when the results from the CoolCap trial were published showing a marginal benefit from cooling. As a result of this, the TOBY trial size was increased. The results of the TOBY trial were remarkably consistent with previous trials.

The most recent systematic review (Jacobs et al. 2013) showed that cooling increases the infants' chance of surviving without neurological deficits at 18 months, reducing neurodevelopmental impairment in survivors. The relative effects of selective head and whole body cooling seemed indistinguishable. In summary the UCL research identified secondary energy failure after neonatal asphyxia, demonstrated the beneficial effects in animal models and illustrated salutary effects in the first clinical trial of brain cooling, later confirmed by many other investigators.

3. References to the research

[1] Lorek A, Takei Y, Cady E, Wyatt J, Penrice J, Edwards A, et al. Delayed ("secondary") cerebral energy failure after acute hypoxia-ischemia in the newborn piglet: continuous 48-hour studies by phosphorus magnetic resonance spectroscopy. Pediatr Res. 1994;36:699-706. http://www.ncbi.nlm.nih.gov/pubmed/7898977

[2] Thoresen M, Penrice J, Lorek A, Cady E, Wylezinska M, Kirkbride V, Cooper C, Brown G, Edwards A, Wyatt J, et al (1995) Mild hypothermia after severe transient hypoxia-ischemia ameliorates delayed cerebral energy failure in the newborn piglet. Pediatr Res 37:667-670. http://dx.doi.org/10.1203/00006450-199505000-00019

[3] Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, Polin RA, Robertson CM, Thoresen M, Whitelaw A, Gunn AJ. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet. 2005 Feb 19-25;365(9460):663-70. http://dx.doi.org/10.1016/S0140-6736(05)17946-X

Funding

The CoolCap trial was funded by Olympic Medical.

4. Details of the impact

Our early work on large animal models underpinned trials undertaken by ourselves and by others, which in turn have resulted in therapeutic hypothermia becoming standard care for infants with moderate to severe neonatal encephalopathy. The importance of the early work at UCL in particular, as the basis for later work and impacts was described in detail in a recent article **[a]**. As a result of these important international collaborations, over 3,000 infants so far in the UK have benefitted from this treatment, which was incorporated into NICE guidance in 2010. Our work also resulted in the commercial development of the CoolCap.

Immediately following the conclusion of the enrolment of the TOBY Trial, the UK TOBY Cooling Register was set up and was operational between Dec 2006 and Dec 2012. All newborns treated with cooling in the UK have been eligible to be registered. During this time over 3,000 babies cooled at 74 neonatal units were registered, showing how the treatment has been adopted into normal clinical practice **[b]**. Analysis of these data in 2012 suggested that the number of babies registered was close to the estimates of all babies suffering from moderate to severe neonatal encephalopathy **[c]**.

The impact on long-term outcomes for these babies is clear. A recent meta-analysis including seven trials and 1,214 infants shows that therapeutic hypothermia results in a reduction in death or major neurodevelopmental disability (risk ratio 0.76; 95% CI 0.69-84) and an increase in the rate of survival with normal neurological function (1.63; 1.36-1.95) at age 18 months **[d]**. Based on the number of infants treated by cooling we can predict that approximately 450 have avoided death or serious neurological disability between 2006 and 2012.

Following our trial of the CoolCap, this device received FDA approval in 2006 **[e]** and has been sold commercially since that time **[f]**. It is now in use in 30 hospitals across the United States (many of them covering a wide geographical area, due to the specialist nature of the services provided) **[g]**.

In 2009, children's charity Bliss endorsed the positive reports from research into cooling: Carmel Bartley, of the children's charity, Bliss said: *"This is welcome research into an area which is known to save lives. It is a specialist treatment we would like to see used more widely"* **[h]**

In 2010, the recommendation for therapeutic hypothermia was incorporated into NICE guidelines **[i]**. The British Association of Perinatal Medicine (BAPM) also recommended this treatment in guidelines issued in the same year **[j]**. Enrolment into the cooling Registry increased dramatically after this, and shows that there has been a timely, systematic implementation of therapeutic hypothermia in the UK to a standard protocol. There has been a steady rise in the uptake of therapeutic hypothermia across the UK. Elsewhere in the world, in October 2010, the International Liaison Committee on Resuscitation (ILCOR) and American Heart Association released its revised statement recommending therapeutic hypothermia as a standard of care for moderate to severe HIE **[k]**.

A health economic study done by Imperial College London set out the clear economic case for this treatment. Using current lifetime costs for each child with cerebral palsy (about £750,000) and the economic benefit of additional healthy lives (£800,000), the total benefit to the UK economy as a result of the implementation of therapeutic hypothermia is likely to be over £125 million so far **[c]**.

5. Sources to corroborate the impact

[a] Edwards AD (2009) The Discovery of Hypothermic Neural Rescue Therapy for Perinatal Hypoxic-Ischemic Encephalopathy. Seminars in Pediatric Neurology 16:4 p.200- 6 http://dx.doi.org/10.1016/j.spen.2009.09.007

[b] TOBY Register https://www.npeu.ox.ac.uk/files/downloads/tobyregister/newsletters/TCR-Closing-Newsletter-December-2012.pdf

[c] Azzopardi D, Strohm B, Linsell L, Hobson A, Juszczak E, Kurinczuk JJ, Brocklehurst P, Edwards AD; UK TOBY Cooling Register. Implementation and conduct of therapeutic hypothermia for perinatal asphyxial encephalopathy in the UK--analysis of national data. PLoS One. 2012;7(6):e38504. http://dx.doi.org/10.1371/journal.pone.0038504.

[d] Tagin MA, Woolcott CG, Vincer MJ, Whyte RK, Stinson DA. Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta-analysis. Arch Pediatr Adolesc Med 166:558-566. Arch Pediatr Adolesc Med. 2012 Jun 1;166(6):558-66. http://dx.doi.org/10.1001/archpediatrics.2011.1772

[e] FDA approval (citing the 2005 study): http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108813.htm

[f] Details of the Olympic CoolCap: http://www.natus.com/index.cfm?page=products_1&crid=115&contentid=207

[g] Dayton Children's Hospital, Ohio, report that 30 hospitals in the US use the device: http://www.childrensdayton.org/cms/resource_library/grand_round_files/377038f863063b6f/index.html. Other examples include:

a. Arkansas Children's Hospital: http://www.archildrens.org/Services/Neonatal-Intensive-Care-Unit/Head-Cooling.aspx

b. Various hospitals in Nebraska – an article in the Omaha World Herald reports "*In the past 2½ years, about 50 children have been treated with the cooling cap at Children's, the Nebraska Medical Center, Creighton University Medical Center and Bergan Mercy Medical Center*." http://www.omaha.com/article/20101006/NEWS01/710069904/1013102

c. The cool-cap is used at Boston Medical Centre, and a cooling blanket is used at

University of California at San Francisco School of Medicine and Children's Hospital Boston http://commonhealth.wbur.org/2012/01/oxygen-deprived-newborns-cool-down/

[h] http://www.independent.co.uk/life-style/health-and-families/health-news/cooling-cure-averts-infant-brain-damage-1795740.html

[i] NICE (2010) National Institute for Clinical Excellence: Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury: guidance NICE guidelines: interventional procedures http://www.nice.org.uk/nicemedia/live/11315/48809/48809.pdf

[j] BAPM guidelines, June 2010: http://www.bapm.org/publications/documents/guidelines/Position_Statement_Therapeutic_Cooling_Neonatal_Encephalopathy_July%202010.pdf

[k] Perlman JM, Wyllie J, Kattwinkel J, Atkins DL, Chameides L, Goldsmith JP, Guinsburg R, Hazinski MF, Morley C, Richmond S, Simon WM, Singhal N, Szyld E, Tamura M, Velaphi S; Neonatal Resuscitation Chapter Collaborators. Part 11: Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation. 2010 Oct 19;122(16 Suppl 2):S516-38. http://dx.doi.org/10.1161/CIRCULATIONAHA.110.971127 Recommends: "*Therapeutic hypothermia should be considered for infants born at term or near-term with evolving moderate to severe hypoxic-ischemic encephalopathy, with protocol and follow-up coordinated through a regional perinatal system*." Cites our study and the others described above.