Institution: University College London / Birkbeck College

Unit of Assessment: 5 - Biological Sciences

Title of case study: Pain relief for hospitalised infants

1. Summary of the impact

Eight per cent of all live births in the UK are preterm. Many of these infants spend time in special care, receiving an average of ten painful procedures per day of hospitalisation. Analgesics are administered to infants on an ad hoc basis and evidence of their efficacy has relied upon observations of behaviour and indirect physiologic responses. Fitzgerald and Slater at UCL have pioneered neurophysiological measurement of pain activity in the human infant brain, based upon Fitzgerald's developmental pain research. Using this measure, they have carried out the first ever randomised clinical trial of neonatal analgesic efficacy using a quantitative neural outcome.

2. Underpinning research

The Fitzgerald lab at the UCL Research Department of Neuroscience, Physiology and Pharmacology has been recognised for many years as a world leader in the neurobiology of infant and childhood pain. Fitzgerald's research into the developmental neurophysiology of neural pathways and circuits that process pain is carried out in animal models and in human subjects. The first studies on human infants focussed upon the measurement of spinal nociceptive reflexes (using electromyography (EMG) recording from flexor muscles of the lower limb), and the sensitisation of these reflexes to repeated skin-breaking procedures and surgery **[1,2]**. Later studies focussed upon activity in the brain, using near-infrared spectroscopy (NIRS) **[3,4]** and electroencephalography (EEG) **[5,6]** to measure cortical activation in response to time-locked, clinically required heel lances used to draw blood for clinical monitoring.

Fitzgerald and colleagues discovered that even the youngest infant displayed a measurable brain activation following a tissue-damaging noxious stimulus, as shown by cortical haemodynamic responses **[3,4]** and specific evoked nociceptive potentials **[5,6]**. Importantly, while there is some correlation between these direct brain measures and the currently used clinical observation tools, it is clear that not all infants are able to display pain facial expressions or physiological responses and that the recorded neural activity in the brain was in many cases a more reliable measure of pain activity **[4]**. The size of the evoked potentials increases with gestational age, and premature infants who have undergone repeated noxious stimuli in intensive care have larger evoked nociceptive potentials than their age-matched counterparts who were born full term **[6]**. This confirmed basic laboratory studies which had shown that repeated noxious stimulation in infancy can lead to prolonged sensitisation of nociceptive circuits and increased pain.

Improving the treatment of pain in infants requires analgesic trials in the infant population with reliable, quantitative outcome measures of pain. The discovery that single heel lances evoke specific nociceptive brain activity recorded with neonatal electroencephalography (EEG) and spinal nociceptive reflexes recorded with electromyography led Fitzgerald and colleagues to use this specific nociceptive brain activity as a direct measure of infant pain in a randomised controlled trial of analgesia.

3. References to the research

[1] Andrews K, Fitzgerald M. The cutaneous withdrawal reflex in human neonates: sensitization, receptive fields, and the effects of contralateral stimulation. *Pain*. 1994 Jan;56(1):95-101. http://dx.doi.org/10.1016/0304-3959(94)90154-6

[2] Andrews K, Fitzgerald M. Wound sensitivity as a measure of analgesic effects following surgery in human neonates and infants. *Pain*. 2002 Sep;99(1-2):185-95.

http://dx.doi.org/10.1016/S0304-3959(02)00100-8

[3] Slater R, Cantarella A, Gallella S, Worley A, Boyd S, Meek J, Fitzgerald M. Cortical pain responses in human infants. *J Neurosci.* 2006 Apr 5;26(14):3662-6. http://dx.doi.org/10.1523/JNEUROSCI.0348-06.2006

[4] Slater R, Cantarella A, Franck L, Meek J, Fitzgerald M. How well do clinical pain assessment tools reflect pain in infants? *PLoS Med.;*5(6):e129. http://dx.doi.org/10.1371/journal.pmed.0050129

[5] Slater R, Worley A, Fabrizi L, Roberts S, Meek J, Boyd S, Fitzgerald M. Evoked potentials generated by noxious stimulation in the human infant brain. *Eur J Pain*. 2010 Mar;14(3):321-6. http://dx.doi.org/10.1016/j.ejpain.2009.05.005

[6] Slater R, Fabrizi L, Worley A, Meek J, Boyd S, Fitzgerald M. Premature infants display increased noxious-evoked neuronal activity in the brain compared to healthy age-matched term-born infants. *Neuroimage*. 2010 Aug 15;52(2):583-9. http://dx.doi.org/10.1016/j.neuroimage.2010.04.253

MRC project (Fitzgerald with Boyd, Meek & Worley) 'Cortical responses to pain in human infants - towards a rational analgesic strategy'. Ref: G0502146; £973,367; Jan 2006-Feb 2009.

4. Details of the impact

In the UK, eight per cent of all live births are preterm and many of these infants will spend time in a special neonatal hospital unit receiving medical care. This care necessarily involves repeated invasive procedures, a median of ten painful procedures per hospitalised day. Despite this, pain in this patient group is undertreated and there is an acknowledged need to formulate a scientifically sound, evidence-based, and clinically useful framework for the management of anaesthesia and analgesia in neonates. A major challenge in analgesic trials in the infant population is the definition of a reliable, quantitative outcome measurement of pain. The most commonly used measures are based on behavioural and physiological observations, or composite pain measurement instruments, such as the premature infant pain profile (PIPP), based on these observations. These methods are unlikely to be an appropriate outcome measure for neonatal analgesic trials because they are largely based on human observation and judgment and take no account of the developmental changes in infant motor behaviour.

The discovery by Fitzgerald and colleagues that single heel lances (required for clinical care) in hospitalised infants evoke specific nociceptive brain activity (recorded with neonatal electroencephalography, EEG) and spinal nociceptive reflexes (recorded with electromyography, EMG) meant that these responses could be used as the first quantitative neural measure of pain processing in this vulnerable patient group. For the first time, a randomised controlled analgesic trial in newborn infants was undertaken, using specific nociceptive brain activity as a direct measure of infant pain. The results showed that oral sucrose, a commonly used 'analgesic' for procedural pain in infants does not significantly affect activity in neonatal brain or spinal cord nociceptive circuits, and therefore is unlikely to be an effective analgesic drug. The ability of sucrose to reduce clinical observational scores after noxious events in newborn infants should not be interpreted as pain relief **[a]**.

This trial, listed on the UK trials gateway **[b]**, showed that current analgesic methods in use in neonatal care units around the UK and elsewhere are inadequate and a more rational basis of care is required in the future for this vulnerable patient group.

As is common for big impact clinical papers, the Lancet invited commentaries on the results of this trial **[c]** and a reply to these was also published **[d]**. Importantly the trial received a very positive review on NHS Choices **[e]**.

Evidence that the trial has changed views and practice Professor Chris Kennard, Chair of the MRC's Neuroscience and Mental Health funding board said: "This trial has significant implications for healthcare policy and is a first class example of where MRC research is helping bring scientific discoveries from laboratory bench to patient bedside more quickly. With uncertainty around the role that pain plays in a baby's neurodevelopment, this research is a vital tool for informing healthcare decision makers" **[f]**.

Dr Judith Meek, consultant neonatologist at UCLH has discussed changes in practice in the neonatal unit at UCLH as a result of this study **[g]**. Other recent publications, emphasising problems with sucrose, following on from this sucrose trial have now been published **[h]**. It was also reviewed on the Faculty of 1000 website **[i]**, discussed in Nature Medicine **[j]** and reported in the public press and on numerous medical sites in the UK and the USA **[k]**.

Increasing public awareness of science. In 2011, Fitzgerald contributed to the BBC Horizon programme *The Secret World of Pain* which went out to 1.96m viewers **[l]**. A review in the *Guardian* said: "*The film's greatest pleasure was that each painful story was narrated without exploitativeness aforethought, but with the aim of teaching us some science*." This programme, and Fitzgerald's work, were discussed widely in the press and online, including on blogs and patient forums, showing how the work has increased public awareness of this area of research **[m]**.

5. Sources to corroborate the impact

[a] Slater R, Cornelissen L, Fabrizi L, Patten D, Yoxen J, Worley A, Boyd S, Meek J, Fitzgerald M. Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial. Lancet. 2010 Oct 9;376(9748):1225-32. http://dx.doi.org/10.1016/S0140-6736(10)61303-7

[b] Listing on the UK clinical trials gateway http://www.ukctg.nihr.ac.uk/trialdetails/ISRCTN78390996?view=healthprofessional

[c] Lancet invited five commentaries on the trial :- Steed et al., Stevens B et al., Vanhatalo S, Martins Linhares MB et al., and Heaton PA et al., The Lancet, 2011, Jan 1 377, (9759): 25-7 http://www.thelancet.com/journals/lancet/issue/vol377no9759/PIIS0140-6736%2810%29X6162-1

[d] Lancet Reply to commentaries: Slater R Boyd S, Meek J, Fitzgerald M. Oral sucrose for procedural pain in infants — Authors' reply. The Lancet, 2011, Jan 1 377, (9759): 27-8. http://dx.doi.org/10.1016/S0140-6736(10)62334-3

[e] Positive review on NHS Choices http://www.nhs.uk/news/2010/09September/Pages/sugar-not-a-painkiller-for-babies.aspx#

[f] Medical Research Council http://www.mrc.ac.uk/Newspublications/News/MRC007193

[g] Meek J. Options for procedural pain in newborn infants. Arch Dis Child Educ Pract Ed. 2012 Feb;97(1):23-8. http://dx.doi.org/10.1136/archdischild-2011-300508. (This is an international peer-reviewed journal that keeps health professionals and others up to date in all areas of paediatrics.)

[h] Other recent publications, emphasising problems with sucrose, following on from this trial:

- Asmerom Y, Slater L, Boskovic DS, Bahjri K, Holden MS, Phillips R, Deming D, Ashwal S, Fayard E, Angeles DM. Oral sucrose for heel lance increases adenosine triphosphate use and oxidative stress in preterm neonates. J Pediatr. 2013 Jul;163(1):29-35. http://dx.doi.org/10.1016/j.jpeds.2012.12.088

- Wilkinson DJ, Savulescu J, Slater R. Sugaring the pill: ethics and uncertainties in the use of

sucrose for newborn infants. Arch Pediatr Adolesc Med. 2012 Jul 1;166(7):629-33. http://dx.doi.org/10.1001/archpediatrics.2012.352

- Schechter NL. Using sucrose-with eyes wide open. Arch Pediatr Adolesc Med. 2012 Jul 1;166(7):667-9. http://dx.doi.org/10.1001/archpediatrics.2012.563

[i] The trial was reviewed by Faculty of 1000, F1000Prime, http://f1000.com/prime/5080963

[j] Nature Medicine: http://doi.org/bhhw8z

[k] Other reviews

- The Guardian: http://www.guardian.co.uk/science/2010/sep/02/babies-sugar-pain-relief-warning
- CBC News http://www.cbc.ca/news/technology/sugar-won-t-quell-infants-pain-study-1.922917
- Faculty of 1000 http://f1000.com/5080963
- Medscape and Medpage Today http://www.medscape.com/viewarticle/727926 http://www.medpagetoday.com/PainManagement/PainManagement/22005
- Other health blogs http://heathen-hub.com/blog.php?b=564 http://www.redorbit.com/news/health/1912000/study_challenges_pain_relieving_effects_of_sugar

[l] Viewing figures from www.barb.co.uk.

[m] Public and media engagement with BBC Horizon's *Secret World of Pain*:

- Article on blog Suite 101: http://suite101.com/a/pain-why-key-life-experiences-are-as-important-as-genes-a341436
- Patient group, Organisation for the Understanding of Cluster Headache. Discussion of the programme, including Fitzgerald's work highlighting pain and premature babies. http://www.ouchuk.org/forum/viewtopic.php?f=3&t=3457
- Guardian review: http://www.theguardian.com/tv-and-radio/2011/feb/01/tv-review-horizon-episodes