Neonatal pain

Chapter 11

Appendix: Valorization

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1. Relevance to affected patients and their families

The relevance of this thesis on pain management in neonates is best expressed by the Declaration of Montréal, developed by the International Association for the Study of Pain in the year 2010. This Declaration focuses on three issues[1]:

1. The right of all people to have access to pain management without discrimination.

2. The right of people in pain to acknowledgment of their pain and to be informed about how it can be assessed and managed.

3. The right of all people with pain to have access to appropriate assessment and treatment of the pain by adequately trained health care professionals.

Second, in a recent Delphi survey European NICU nurses identified pain and distress as having highest research priorities, indicating insufficient tools to manage neonatal pain in daily practice.[2] In this thesis we addressed these research priorities as well as the Declaration of Montréal.

Part I of this thesis showed chronic pain may exist in the neonate. In our Delphi study consensus was reached on a statement that inadequate pain management may be a risk factor for the development of chronic pain syndromes.[3] Pain in the neonate is routine. Epidemiologic studies consistently show that neonates admitted to an intensive care are subjected to 11-14 painful interventions on average every day.[4-6] A recent survey showed wide variations in pain management and pain assessment in European NICU's exist.[7] This may point to a relevant health care problem, since 15 million babies are born preterm (<37 weeks) worldwide every year.[8] Preterm born infants, accounting for 11.1% of all live births annually[8], frequently require high- or intensive care. If chronic pain in the neonate does exist, at least part of these 15 million preterm babies may be at risk. Since we have shown in an expert panel that there are no objective measures to diagnose chronic pain, this potential problem may even go unnoticed.

Part II of this thesis showed that repeated administration of paracetamol intravenously resulted in a very predictable pharmacokinetic profile in the extreme preterm infant. Furthermore, in our cohort we found no increased liver enzymes and no depletion of glutathione. To date, in literature no short term side effects of paracetamol have been reported when adequately dosed and administered.[9] Opioids have known side effects such as hypotension, decreased intestinal motility and apnea. Clinicians may be reluctant to use opioids due to concerns about these short term effects as well as long term impact on neurodevelopment.[10] Therefore, our results are relevant

such that paracetamol may be an attractive alternative for opioids when systemic analgesia is indicated. The need for identification of non opioid analgesic alternatives has been stressed before.[10] However, dose effect relationships for paracetamol have not yet been established. Types of pain or pain diagnoses for which paracetamol is the most effective treatment option have to be identified.

In part III, we have shown that in the POPS-19 cohort, with the exception of necrotizing enterocolitis, neonatal variables such as gestational age, birth weight, length of stay and sepsis in ex-preterm infants did not modulate experimental pain response or pain coping strategy in adolescence. This might be considered 'good news', however, our findings result from data analyses concerning a cohort born in 1983. Since that time era much has changed in neonatology. The boundaries of viability have shifted significantly after the successful introduction of antenatal corticosteroids and postnatal surfactant administration for respiratory distress syndrome. In the Netherlands, preterm infants born after 23-24 weeks gestation are treated nowadays. The youngest infant in our cohort was 25 weeks, and the total number of infants born with a gestational age < 26 weeks was [11]. In contrast, during a period ranging from 1 October 2010 – 1 October 2011 a total of 105 preterm infants with a gestational age of 25 weeks up to 25 weeks and 6 days were admitted to the Dutch NICU's.[11] Furthermore, 80 preterm infants of 24-25 weeks and 7 infants with a gestational age from 23-24 weeks were admitted.[11] These numbers show an almost 18 fold increase in extremely preterm infants that are subjected to intensive care, hence to painful procedures.
On the other hand, pain management has changed from virtually nothing in 1983 to pain assessment on a daily basis and the use of analgesics in infants with high pain scores or predefined pain diagnosis. If a study such as POPS were to be repeated in current time, results may be different. However, a large follow up study such as POPS is difficult and expensive to repeat. A follow up study with respect to pain may be more cost efficient. We suggest detailed digital registration of pain diagnoses, pain medication and pain scores from the neonatal period. Follow up at regular intervals up to primary school age should include items referring to pain, such as pain coping strategy, the use of analgesics and prevalence of all types of pain beyond the neonatal period. With the help of these detailed data, we may provide the opportunity to assess more in detail the possible association between neonatal pain and long term sequelae, especially in the (extreme) preterm infant.

2. Innovation

Our study on chronic pain emphasizes the need for adequate pain treatment and therefore pain assessment. The results from our expert panel suggest that to date there is no pain scale that can measure chronic pain with sufficient sensitivity and specificity. In fact, recently it was suggested that the behavioral changes that are used with current acute pain assessment tools are consistent with brainstem reflexes, not pain experience.[12] Researchers have advocated the use of integrated

measures, such as near infrared spectroscopy (NIRS), amplitude integrated electroencephalography (aEEG) and Skin Conductance measurements in conjunction with video observations and measurement of autonomic response.[12,13] Modern innovations such as unobtrusive monitoring techniques may provide opportunities for such an integration. Non invasive ECG monitoring techniques already exist.[14] Preterm infants with respiratory support often wear caps for fixation of respiratory support devices. It is a challenge to integrate NIRS and aEEG sensors in these caps while at the same time not interfering with the comfort of these infants. Automated facial detection is being developed and has shown to have 85% sensitivity and 100% specificity in resting state, while showing 100% sensitivity and specificity during painful procedures.[15] Inter-'observer' reliability between trained observers using a validated pain measure and an automated system showed a Cohen's kappa of 0.975, indicating excellent agreement.[15] An experimental version of a sock with which changes in skin conduction as a proxy for stress can be detected was developed in recent years by students of the Technical University in Eindhoven, The Netherlands. This sock, however, has not yet found its way in scientific studies. All these innovations may provide the means for non invasive, integrated measurement of signs of pain and stress.

However, the main concern may be that these methods of detecting pain only reflect part of the pain experience. Structures deep inside the brain, such as the thalamic nuclei and the limbic system, play an important role in the emotional attributes of pain.[16] NIRS and aEEG are not capable of measuring changes in cerebral oxygenation or electroencephalographic changes deep inside the brain, respectively. We do not know how well developed these structures are in the preterm infant, and if aspects such as underdeveloped myelinization in the preterm infant contribute to altered pain experience. Studies investigating the feasibility of functional Magnetic Resonance Imaging (fMRI) to detect pain signal processing in term neonates show both similarities and differences compared to adult signal processing.[17] Therefore, fMRI seems promising in detecting signal processing in deeper brain structures even in neonates. However, results are partly influenced by the sedation often needed with neonatal MRI studies.[17] On an experimental basis, integration of fMRI, aEEG, NIRS and Skin Conductance measurements may provide insight in activation of brain regions responsible for pain experience in neonates and preterm infants. This integration may further our understanding of the associations between pain behavior and emotional aspects of neonatal pain.

Software development of Electronic Patient Data Management Systems (ePDMS) should provide easy recording and analysis of pain associated events. Pain diagnoses, pain assessment scores and pain medication are available in PDMS, but these data are not integrated. For research purposes a PDMS should have the possibility to easy access these data and export them for further offline analysis. These data can be used in follow up programs to assess possible associations between neonatal pain and altered pain response, pain behavior or even increased or decreased use of Health Care resources related to pain. In the Netherlands perinatal data is being recorded by the 'Stichting Perinatale Registratie Nederland' or 'Dutch Foundation for

Perinatal Registration'. These data are predominantly being used for epidemiologic analysis, but, when extended with data on neonatal pain, could provide the necessary demographic and clinical data that are needed for research on long term effects of neonatal pain.
Follow up programs in the 10 Dutch NICU's vary, but all programs provide physical examination, psychological evaluation and physiotherapy. The follow up program is aimed at early detection of neurodevelopmental and motor developmental problems in NICU graduates. This program provides an excellent opportunity to gain insight in pain related problems at different points in time. These problems may comprise pain related complaints such as tummy pain, headache, increased or decreased pain sensitivity, use of pain medication, absence from school due to pain, and the use of adaptive or maladaptive pain coping styles. The follow up program may, in the future, be useful to help parents understand pain related problems of NICU graduates later in life, and cope with them.

3. Ultimate goal and a road map

In summary, the ultimate goal of pain research in neonates is to provide a) the means to detect pain behavior and pain experience accurately, and b) to treat pain adequately without short- and long term side effects.
In order to achieve these goals we first need to determine what signs & symptoms best reflect neonatal pain. In the innovation paragraph we highlighted possibilities to investigate signs and symptoms that reflect pain experience, rather than pain behavior. Based on these sort of data we can evaluate existing pain assessment tools or develop a feasible pain assessment tool for daily practice, in order to detect the different types of pain (acute/procedural, chronic, visceral, neuropathic and so on). In the ideal world, such a pain tool would measure continuously, simply because (preterm) neonates cannot verbally indicate they are in pain at any given point in time, or maybe to sick to give any signal at all. This calls for an automated process. Since we are still at the beginning of our understanding of true pain experience in neonates, it may well take years (if not decades) before such a process has been developed.
Pain management should be based on accurate pain measurement. It should comprise both safe and effective pharmacologic as well as non-pharmacologic therapy. While we have shown that repeated doses of paracetamol intravenously has no effect on glutathione levels or liver enzymes, we did not investigate long term adverse effects. A recent review summarized the available evidence concerning long term safety of paracetamol administration during pregnancy and early childhood. While animal studies suggest paracetamol to have adverse effects on neurodevelopment, long term follow up studies in humans only show (at best) a moderate effect in prevalence of attention deficit and hyperactivity disorders that may be explained by confounding.[18] However, a prospective clinical study combining pharmacodynamic attributes of paracetamol and long term follow up is needed. This study, again, would fit in the long term follow up programs in use today in The Netherlands. Such a study

could easily comprise other pharmacologic and non pharmacologic therapeutic options such as opioids, sucrose, facilitated tucking and kangaroo care. The effects of these therapeutic options on the developing infant has to be evaluated as part of long term follow up. We therefore advocate the development of a digital database comprising of neonatal data with respect to pain assessment and pain management, and the integration of pain related follow up data in the Dutch follow up program. This database may then provide the opportunity to answer the question whether pain and treatment of pain has adverse long term effects that cannot be explained by the many confounding factors during the development of an infant.

REFERENCES

1. IASP. Declaration of Montréal. 2010. http://www.iasp-pain.org/files/Content/NavigationMenu/Advocacy/DeclarationOfMontreal.pdf. Accessed june 2016.
2. Wielenga JM, Tume LN, Latour JM, van den Hoogen A. European neonatal intensive care nursing research priorities: An e-delphi study. *Arch Dis Child Fetal Neonatal Ed.* 2015;100(1):F66-71.
3. van Ganzewinkel CJ, Anand KJ, Kramer BW, Andriessen P. Chronic pain in the newborn: Toward a definition. *Clin J Pain.* 2014;30(11):970-977.
4. Carbajal R, Rousset A, Danan C, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. *JAMA*. 2008;300(1):60-70.
5. Roofthooft DW, Simons SH, Anand KJ, Tibboel D, van Dijk M. Eight years later, are we still hurting newborn infants? *Neonatology.* 2014;105(3):218-226.
6. Simons S, van Dijk M, Anand K, Roofthooft D, van Lingen R, Tibboel D. Do we still hurt newborn babies? A prospective study of procedural pain and analgesia in neonates. *Arch Pediatr Adolesc Med*. 2003;157(11):1058-1064.
7. Carbajal R, Eriksson M, Courtois E, et al. Sedation and analgesia practices in neonatal intensive care units (EUROPAIN): Results from a prospective cohort study. *Lancet Respir Med.* 2015;3(10):796-812.
8. Blencowe H, Cousens S, Chou D, et al. Born too soon: The global epidemiology of 15 million preterm births. *Reprod Health.* 2013;10 Suppl 1:S2-4755-10-S1-S2. Epub 2013 Nov 15.
9. Cuzzolin L, Antonucci R, Fanos V. Paracetamol (acetaminophen) efficacy and safety in the newborn. *Curr Drug Metab.* 2013;14(2):178-185.
10. McPherson C, Grunau RE. Neonatal pain control and neurologic effects of anesthetics and sedatives in preterm infants. *Clin Perinatol.* 2014;41(1):209-227.
11. de Kluiver E, Offringa M, Walther FJ, Duvekot JJ, de Laat MW, Implementatiegroep Richtlijn Extreem Prematuren. Perinatal policy in cases of extreme prematurity; an investigation into the implementation of the guidelines. *Ned Tijdschr Geneeskd.* 2013;157(38):A6362.
12. Fitzgerald M. What do we really know about newborn infant pain? *Exp Physiol.* 2015;100(12):1451-1457.
13. Worley A, Fabrizi L, Boyd S, Slater R. Multi-modal pain measurements in infants. *J Neurosci Methods.* 2012;205(2):252-257.
14. Atallah L, Serteyn A, Meftah M, et al. Unobtrusive ECG monitoring in the NICU using a capacitive sensing array. *Physiol Meas*. 2014;35(5):895-913.
15. Heiderich TM, Leslie AT, Guinsburg R. Neonatal procedural pain can be assessed by computer software that has good sensitivity and specificity to detect facial movements. *Acta Paediatr.* 2015;104(2):e63-9.
16. Fabbro F, Crescentini C. Facing the experience of pain: A neuropsychological perspective. *Phys Life Rev*. 2014;11(3):540-552.
17. Williams G, Fabrizi L, Meek J, et al. Functional magnetic resonance imaging can be used to explore tactile and nociceptive processing in the infant brain. *Acta Paediatr.* 2015;104(2):158-166.
18. de Fays L, Van Malderen K, De Smet K, et al. Use of paracetamol during pregnancy and child neurological development. *Dev Med Child Neurol.* 2015;57(8):718-724.