

Impact of Recurring Technical Pain-Associated Stress in Preterm Infants

Denisa Bego (Veseli)¹

Ferit Zavalani²

Rudina Pirushi³

Enkelejda Shkurti⁴

Diamant Shtiza⁵

^{1,3,4} Faculty of Technical Medical Sciences, University of Medicine, Tirana, Albania

^{2,5} University Hospital Centre : "Mother Theresa", Tirana Albania

Doi:10.5901/ajis.2015.v4n1p411

Abstract

The mainstream of babies born very preterm currently stay alive, nevertheless, lasting neurodevelopment and behavioral issues remain a distress. As a component of their neonatal care very preterm babies experience frequent painful processes throughout a stage of quick brain growth and programming of stress structures. Aim/methods This review was conducted to distinguish and to manage pain related stress in preterm infants. These premature babies born so early have the capacity to recognize pain, conversely, their sensory structures are functionally undeveloped. An disparity of excitatory against inhibitory procedures brings about amplified nociceptive signs in the central nervous system. Detailed cell populations in the central nervous system of premature babies are mainly susceptible to oxidative pressure and inflammation. Results Neonatal rat patterns have revealed that constant pain raises apoptosis of neurons, and neonatal pain and stress cause restless behaviors through maturity. In human creatures, bigger exposure to neonatal pain-associated stress has been connected with distorted brain microstructure in addition to reduced cognitive, motor and behavioral neurodevelopment in premature babies. Conclusions It is essential that pain-correlated stress in preterm neonates is precisely recognized, correctly handled, and that pain supervision approaches are assessed for protective or unfavorable results in the long term.

Keywords: Pain- associated stress, preterm infants,

1. Introduction

Preterm babies, particularly those born among 24–32 weeks GA are exposed to continual technical pain-connected stress, through a stage of physiological susceptibility and fast brain advance, as component of their life-reduction care.

Preterm babies have the necessary nociceptive circuitry to recognize pain, though, this system is functionally undeveloped (Fitzgerald M 2005; Fitzgerald M, Walker SM 2009). Membrane receptive areas are huge in the neonate and marginal sensory fibers are aware to tissue damage and have reduced peak dismissal rates (Li J, Walker SM, Fitzgerald M 2009). Axon terminals provisionally go beyond in lamina II of the spinal cord with low-threshold detectable involvements, making it harder for neonates to differentiate among injurious and non - injurious stimuli (Beggs S, Torsney C 2002; Granmo M 2008). Therefore, before 35 weeks development infants expose central sensitization to persistent measures (Andrews K 1994; Fitzgerald M, Millard C 1989; Walker SM 2009). This alteration has been verified by electrophysiological (EEG) recordings, since reactions to heel lance were dissolved neuronal ruptures in preterm babies contrary to the modality-detailed localized, suggested potentials noted at ~36 weeks postmenstrual period (Fabrizi L, Slater R 2011). Furthermore, modifications in the EEG recordings of preterm neonates stand for the vanishing of the radial glia and enhance in involvedness of the brainy cortex (McKinstry RC 2002; Vinall J & Grunau RE 2013). Nonetheless, sliding intonation of nociceptive motion in the dorsal horn of the spinal cord expands afterward, further than term correspondent age (Van Praag H, Frenk H 1991; Hathway GJ 2009).

Neonatal pain appraisal tools rule a diversity of behavioral and physiological reactions (e.g. facial strokes, weep, heart speed, respiratory rate and oxygen diffusion) to facilitate measuring pain in nonverbal subjects (Holsti L, Grunau RE 2008; Stevens BJ 1993).

Conversely, these markers are not precise to pain, and may as well symbolize disturbance or sorrow reactions to

neonatal pain also differ based on sleep-get up condition, disease harshness, plus extent of earlier revelations to pain and non-insidious interferences (Grunau RE, Oberlander TF 2001; Holsti L, Grunau RE 2006, Ranger M, Johnston CC 2007).

Consequently, health professionals are faced with the hard assignment of discerning and suitably handling pain in preterm babies. Dampened behavioral and physiological responses to pain do not necessarily represent absence of nociceptive processing in the CNS (Slater R *et al* 2010; Slater R & Cornelissen L 2010).

Pharmacological care is not ideal for routine pain management (Carbajal R, Lenclen R 2005), and while non-pharmacologic management is recommended as a first step, often invasive procedures in the NICU are still performed without support (Johnston C, Barrington KJ 2011). Unmanaged pain may have substantive effects on the developing brain and stress systems of premature neonates, however, pain management remains a challenge.

2. Methodology

The transcription of genes all over the body and the brain is controlled by stress hormones (Chrousos GP *et al* 2009). As a result, extended start of the HPA axis in physiologically undeveloped infants, can bring about lasting alterations in hormonal, physiological and behavioral structures (Coplan JD, Andrews MW 1996 Meaney MJ *et al* 1996). Nevertheless, in very preterm neonates their cortisol ranks are commonly lower than predicted, taking into account the amount of procedures needed through their hospitalization (Peters KL *et al* 1998). This may signify an collapse of supplies between these physiologically undeveloped infants immaturity of the adrenal cortex or other issues in this therapeutic framework. Larger revelation to painful processes has been related with the rearrangement of the stress hormone scheme. Grunau *et al* (2005) established that bigger increasing neonatal technical pain revelation was related with inferior cortisol reactions to stress at 32 weeks postmenstrual period, free of premature disease harshness and morphine coverage, and not reported for by GA at delivery (Grunau RE & Holsti L 2005). On the contrary, in neonates born at particularly low gestational period (ELGA: 24–28 weeks gestation) at 8 and 18 months approved age (CA) cortisol ranks were raised, as a consequence of revelation to elevated figures of skin-breaking processes from delivery to term corresponding age (Grunau RE & Weinberg J 2004). Between neonates born ELGA there are data for a transfer from low basal cortisol ranks at 3 months to moderately elevated levels at 8 and 18 months CA, that implies a biological "rearrangement" of endocrine stress structures (Grunau RE & Haley DW 2007).

Sub plate neurons and pre-oligodendrocytes are equally mostly vulnerable populations that cause harm in the premature brain (Volpe JJ *et al* 2009). Sub plate neurons are between the first cells generated in the mammalian cerebral cortex. They are the chief cortical neurons to acquire excitatory synaptic inputs from thalamic axons, establishing a temporary connection between thalamic axons and their final objective in the cerebral cortex (Kostovic I *et al* 2002; McQuillen PS, Ferriero DM). Glutamate n methyl-D-aspartate (NMDA) receptors involved in the transmission of the pain marker are more active during early life as a result of the developmentally delayed manifestation of NR2A receptor sub units matched up to NR2B.

Accordingly, recurrent pain may instigate apoptosis of the sub plate neurons previous to the intense ejection of glutamate and incursions of calcium (Qu Y, Vadivelu S, Choi L, *et al* 2003; Deng W, Rosenberg PA 2003). The immaturity of oligodendrocytes makes them principally exposed to instantaneous oxygen, nitrogen species and cytokines generated by microglia (Back SA, Gan X, Li Y 1998; Pang Y & Cai Z, 2005). Ritual pain stimulates jointly oxidative stress and inflammatory reactions (Slater L, Asmerom Y, Boskovic DS 2012; Hansson E 2006). Therefore it may detain the development of pre-myelinating cells.

3. Results

Larger infant ache-linked stress has been related with minor cognitive and motor role at 8 and 18 months proper age, and elevated internalizing (anxious/depressed) performance at 18 months accurate age and at age 7 years (Grunau RE, Whitfield MF 2009; Ranger M, Synnes AR, Vinall J 2013). Though, pain experience may not adjust lasting effects of preterm babies. Between children born ELGA, increasing infant pain-correlated stress was allied with alterations in immediate brain movement at school-period, and these changes in brain fluctuations were harmfully connected with visual-perceptual capabilities (Doesburg SM *et al* 2013). Hence, it emerges that the pressure of infant pain-allied stress on lasting cognitive effects might be during distorted brain role amid children born ELGA.

Recently, studies have primarily exposed that procedural stress in preterm infants is associated with abnormal brain development during neonatal intensive care (Brummelte S, Grunau RE 2012, Smith GC, Gutovich J 2011). These

outcomes are maintained by records from animal models that have stated both inflammatory pain and stable injections to elevate apoptosis in the neonatal rat brain (Anand KJ & Garg S 2007; Duhrsen L & Simons SH 2013). Afterward, recurring focus to procedural ache appears to impact neonatal brain development. Furthermore, between neonates born ELGA, larger revelation to infant pain-associated stress was as well linked with modifications in immediate neuro-magnetic motion (Doesburg SM, Chau CM 2013). Hence, it emerges that continual spotlight to infant procedural stress is allied to lasting adjustments to neuronal composition and role.

Significantly, correlations among infant pain-associated stress and brain maturity also seems to expand further than the affiliations examined in early existence (Brummelte S et al 2012, Zwicker JG 2013). Elevated figures of skin-flouting procedures were linked with leaner cortical gray substance in 21 beyond 66 cerebral areas evaluated at 7 years of age, mostly involving the frontal and parietal lobes (Duhrsen L, Simons SH, Dzierko M 2013).

4. Conclusions

Pharmacological and environmental sustain approaches for pain administration are commonly applied in the NICU (Neonatal Intensive Care Unit). Pharmacological management of pain, and probable continuing outcomes of pain relievers, anesthetics and sedatives are composite issues that have been lately evaluated somewhere else (Anand KJ 2007 Marlow N et al 2014). Because of distresses concerning temporary and probable long-standing results of pharmacological instruments, recent proposals are that opiates and sedatives might be utilized cautiously in the NICU for non-surgical ache supervision of ventilated preterm infants (Bellù R & de Waal KA 2008, Batton DG, Barrington KJ 2006). A numeral of environmental (non-pharmacologic) intrusions are applied for the administration of habitual sharp ritual pain in the NICU (Pillai Riddell RR & Racine NM et al 2011; Stevens B & Yamada J 2013).

Nowadays sucrose is the main commonly applied non-pharmacologic intercession for the healing of slight procedures in preterm neonates (Milgrom J et al 2010). Nevertheless, whereas it is well-recognized that oral sucrose decreases behavioral replies and occasionally physiological reactions (Taddio A & Yiu A 2009), sucrose does not seem to diminish EEG reaction to pain (Slater R & Worley A 2010). It is essential for prospect surveys to observe the degree to which diverse pain administration strategies may be brain defensive.

Parent sustain to encourage sensitive and approachable relations through hospitalization of preterm neonates in the NICU seems to develop white substance maturation (Milgrom J et al 2010).

Additionally, in ELGA neonates, affirmative maternal communication at 18 months CA was related with minor cortisol ranks (Brummelte S & Grunau RE 2011). Helpful parent communication at 18 months CA seemed to improve depressing outcomes of neonatal ache on stress-receptive behaviors (Vinall J & Miller SP 2013). For that reason, whereas more exploration is required to adjust pain management approaches in the NICU, it is hopeful that primary studies recommend that receptive and approachable care-giving seems to improve some outcomes of infant-pain correlated pressure on brain, stress and behavioral effects.

5. Recommendations

Contact to recurring infant pain-associated stress is linked with distorted brain growth, role and neuro-developmental result in preterm infants.

Consequently, it is of the greatest significance that pain-correlated stress in preterm neonates is exactly recognized and suitably handled. Ache management is requisite for human care of neonates; though, there are main gaps in comprehension as to which administration intercessions may be brain defensive and to what level.

References

- Fitzgerald M 2005. The development of nociceptive circuits. *Nat Rev Neurosci*; 6:507–520. [PubMed: 15995722]
- Fitzgerald M, Walker SM 2009. Infant pain management: a developmental neurobiological approach. *Nat Clin Pract Neurol.*; 5:35–50. [PubMed: 19129789]
- Andrews K, Fitzgerald M 1994. The cutaneous withdrawal reflex in human neonates: sensitization, receptive fields, and the effects of contralateral stimulation. *Pain.*; 56:95–101. [PubMed: 8159446]
- Jennings E, Fitzgerald M 1998. Postnatal changes in responses of rat dorsal horn cells to afferent stimulation: a fibre-induced sensitization. *J Physiol.*; 509(Pt 3):859–868. [PubMed: 9596805]
- Li J, Walker SM, Fitzgerald M, Baccei ML 2009. Activity-dependent modulation of glutamatergic signaling in the developing rat dorsal horn by early tissue injury. *J Neurophysio*; 102:2208–2219. [PubMed: 19675290]

- Beggs S, Torsney C, Drew LJ, Fitzgerald M 2002. The postnatal reorganization of primary afferent input and dorsal horn cell receptive fields in the rat spinal cord is an activity-dependent process. *Eur J Neurosci* ; 16:1249-1258. [PubMed: 12405985]
- Granmo M, Petersson P, Schouenborg J 2008. Action-based body maps in the spinal cord emerge from a transitory floating organization. *J Neurosci.*; 28:5494-5503. [PubMed: 18495883]
- Fitzgerald M, Millard C, McIntosh N 1989. Cutaneous hypersensitivity following peripheral tissue damage in newborn infants and its reversal with topical anaesthesia. *Pain.*; 39:31-36. [PubMed: 2812853]
- Grunau RE, Oberlander TF, Whitfield MF, Fitzgerald C, Lee SK 2001. Demographic and therapeutic determinants of pain reactivity in very low birth weight neonates at 32 Weeks' postconceptional Age. *Pediatrics*; 107:105-112. [PubMed: 11134442]
- Holsti L, Grunau RE, Oberlander TF, Whitfield MF 2005. Prior pain induces heightened motor responses during clustered care in preterm infants in the NICU. *Early Hum Dev.*; 81:293-302. [PubMed: 15814212]
- Holsti L, Grunau RE, Whitfield MF, Oberlander TF, Lindh V 2006. Behavioral responses to pain are heightened after clustered care in preterm infants born between 30 and 32 weeks gestational age. *Clin J Pain.*; 22:757-764. [PubMed: 17057556]
- Walker SM, Tochiki KK, Fitzgerald M. 2009. Hindpaw incision in early life increases the hyperalgesic response to repeat surgical injury: critical period and dependence on initial afferent activity. *Pain* ; 147:99-106. [PubMed: 19781855]
- Fabrizi L, Slater R, Worley A, et al 2011. A shift in sensory processing that enables the developing human brain to discriminate touch from pain. *Curr Biol* ; 21:1552-1558. [PubMed: 21906948]
- McKinstry RC, Mathur A, Miller JH, et al 2002. Radial organization of developing preterm human cerebral cortex revealed by non-invasive water diffusion anisotropy MRI. *Cereb Cortex*; 12:1237-1243. [PubMed: 12427675]
- Vinall J, Grunau RE, Brant R, et al 2013. Slower postnatal growth is associated with delayed cerebral cortical maturation in preterm newborns. *Sci Transl Med.*; 5:168ra8.
- Van Praag H, Frenk H 1991. The development of stimulation-produced analgesia (SPA) in the rat. *Brain Res Dev Brain Res*; 64:71-76.
- Hathway GJ, Koch S, Low L, Fitzgerald M 2009; The changing balance of brainstem-spinal cord modulation of pain processing over the first weeks of rat postnatal life. *J Physiol.* 587:2927-2935. [PubMed: 19403624]
- Holsti L, Grunau RE, Oberlander TF, Osioviich H. 2008 Is it painful or not? Discriminant validity of the Behavioral Indicators of Infant Pain (BIIP) scale. *Clin J Pain*; 24:83-88. [PubMed: 18180641]
- Stevens BJ, Johnston CC, Horton L 1993. Multidimensional pain assessment in premature neonates: a pilot study. *J Obstet Gynecol Neonatal Nurs*; 22:531-541.
- Ranger M, Johnston CC, Anand KJ 2007. Current controversies regarding pain assessment in neonates. *Semin Perinatol* ; 31:283-288. [PubMed: 17905182]
- Van Dijk M, Tibboel D 2012. Update on pain assessment in sick neonates and infants. *Pediatr Clin North Am* ; 59:1167-1181. [PubMed: 23036250]
- Slater R, Worley A, Fabrizi L, et al 2010. Evoked potentials generated by noxious stimulation in the human infant brain. *Eur J Pain* ; 14:321-326. [PubMed: 19481484]
- Slater R, Cornelissen L, Fabrizi L, et al.2010. Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial. *Lancet* ; 376:1225-1232. [PubMed: 20817247]
- Carbajal R, Lenclen R, Jugie M, Paupe A, Barton BA, Anand KJ 2005. Morphine does not provide adequate analgesia for acute procedural pain among preterm neonates. *Pediatrics.*; 115:1494-1500. [PubMed: 15930209]
- Johnston C, Barrington KJ, Taddio A, Carbajal R, Filion F 2011. Pain in Canadian NICUs: have we improved over the past 12 years *Clin J Pain*; 27:225-232. [PubMed: 21178602]
- Chrousos GP 2009. Stress and disorders of the stress system. *Nat Rev Endocrinol* ; 5:374-381. [PubMed: 19488073]
- Coplan JD, Andrews MW, Rosenblum LA, et al 1996. Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early-life stressors: implications for the pathophysiology of mood and anxiety disorders. *Proc Natl Acad Sci USA* ; 93:1619-1623. [PubMed: 8643680]
- Lupien SJ, McEwen BS, Gunnar MR, Heim C 2009. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci* ; 10:434-445. [PubMed: 19401723]
- Heim C, Nemeroff CB 2002. Neurobiology of early life stress: clinical studies. *Semin Clin Neuropsychiatry* ; 7:147-159. [PubMed: 11953939]
- Meaney MJ, Diorio J, Francis D, et al 1996. Early environmental regulation of forebrain glucocorticoid receptor gene expression: implications for adrenocortical responses to stress. *Dev Neurosci*; 18:49-72. [PubMed: 8840086]
- Peters KL 1998. Neonatal stress reactivity and cortisol. *J Perinat Neonatal Nurs.*; 11:45-59. [PubMed: 9592461]
- Grunau RE, Holsti L, Haley DW, et al 2005. Neonatal procedural pain exposure predicts lower cortisol and behavioral reactivity in preterm infants in the NICU. *Pain* ; 113:293-300. [PubMed: 15661436] Vinall and Grunau Page 6
- Grunau RE, Weinberg J, Whitfield MF 2004. Neonatal procedural pain and preterm infant cortisol response to novelty at 8 months. *Pediatrics* ; 114:e77-84. [PubMed: 15231977]
- Grunau RE, Haley DW, Whitfield MF, Weinberg J, Yu W, Thiessen P 2007. Altered basal cortisol levels at 3, 6, 8 and 18 months in infants born at extremely low gestational age. *J Pediatr* ; 150:151-156. [PubMed: 17236892]
- Volpe JJ 2009. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol* ; 8:110-124. [PubMed: 19081519]
- Kostovic I, Judas M, Rados M, Hrabac P 2002. Laminar organization of the human fetal cerebrum revealed by histochemical markers and magnetic resonance imaging. *Cereb Cortex.*; 12:536-544. [PubMed: 11950771]

- Kostovic I, Judas M 2002. Correlation between the sequential ingrowth of afferents and transient patterns of cortical lamination in preterm infants. *Anat Rec* ; 267:1–6. [PubMed: 11984786]
- McQuillen PS, Ferriero DM 2005. Perinatal subplate neuron injury: implications for cortical development and plasticity. *Brain Pathol* ; 15:250–260. [PubMed: 16196392]
- Qu Y, Vadivelu S, Choi L, et al 2003; Neurons derived from embryonic stem (ES) cells resemble normal neurons in their vulnerability to excitotoxic death. *Exp Neurol*. 184:326–336. [PubMed: 14637103]
- McDonald JW, Johnston MV. Physiological and pathophysiological roles of excitatory amino acids during central nervous system development. *Brain Res Brain Res Rev*. 1990; 15:41–70. [PubMed: 2163714]
- Talos DM, Follett PL, Folkert RD, et al 2006. Developmental regulation of alpha-amino-3-hydroxy-5- methyl-4-isoxazole-propionic acid receptor subunit expression in forebrain and relationship to regional susceptibility to hypoxic/ischemic injury. II. Human cerebral white matter and cortex. *J Comp Neurol* ; 497:61–77. [PubMed: 16680761]
- Deng W, Rosenberg PA, Volpe JJ, Jensen FE 2003. Calcium-permeable AMPA/kainate receptors mediate toxicity and preconditioning by oxygen-glucose deprivation in oligodendrocyte precursors. *Proc Natl Acad Sci USA* 100:6801–6806. [PubMed: 12743362]
- Back SA, Gan X, Li Y, Rosenberg PA, Volpe JJ 1998. Maturation-dependent vulnerability of oligodendrocytes to oxidative stress-induced death caused by glutathione depletion. *J Neurosci* ; 18:6241–6253. [PubMed: 9698317]
- Back SA, Luo NL, Mallinson RA, et al 2005. Selective vulnerability of preterm white matter to oxidative damage defined by F2-isoprostanes. *Ann Neurol* ; 58:108–120. [PubMed: 15984031]
- Haynes RL, Folkert RD, Keefe RJ, et al 2003. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. *J Neuropathol Exp Neurol*; 62:441–450. [PubMed: 12769184]
- Buntinx M, Moreels M, Vandenabeele F, et al 2004. Cytokine-induced cell death in human oligodendroglial cell lines: I. Synergistic effects of IFN-gamma and TNF-alpha on apoptosis. *J Neurosci Res* ; 76:834–845. [PubMed: 15160395]
- Pang Y, Cai Z, Rhodes PG 2005. Effect of tumor necrosis factor-alpha on developing optic nerve oligodendrocytes in culture. *J Neurosci Res*; 80:226–234. [PubMed: 15765524]
- Slater L, Asmerom Y, Boskovic DS, et al 2012. Procedural pain and oxidative stress in premature neonates. *J Pain* ; 13:590–597. [PubMed: 22543043]
- Hansson E 2006. Could chronic pain and spread of pain sensation be induced and maintained by glial activation? *Acta Physiol (Oxf)*; 187:321–327. [PubMed: 16734769]
- Brummelte S, Grunau RE, Chau V, et al. 2012. Procedural pain and brain development in premature newborns. *Ann Neurol*; 71:385–396. [PubMed: 22374882]
- Smith GC, Gutovich J, Smyser C, et al 2011. Neonatal intensive care unit stress is associated with brain development in preterm infants. *Ann Neurol* ; 70:541–549. [PubMed: 21976396]
- Anand KJ, Garg S, Rovnaghi CR, Narsinghani U, Bhutta AT, Hall RW. 2007. Ketamine reduces the cell death following inflammatory pain in newborn rat brain. *Pediatr Res*; 62:283–290. [PubMed: 17551412]
- Duhrsen L, Simons SH, Dzielko M, et al 2013. Effects of repetitive exposure to pain and morphine treatment on the neonatal rat brain. *Neonatology*; 103:35–43. [PubMed: 23037996]
- Zwicker JG, Grunau RE, Adams E, et al 2013. Score for neonatal acute physiology-II and neonatal pain predict corticospinal tract development in premature newborns. *Pediatr Neurol* ; 48:123–129. e1. [PubMed: 23337005]
- Ranger M, Chau CMY, Garg A, et al 2013. Neonatal pain-related stress predicts cortical thickness at age 7 years in children born very preterm. *PLoS ONE* ; 8(10):e76702. [PubMed: 24204657]
- Doesburg SM, Chau CM, Cheung TP, et al. 2013. Neonatal pain-related stress, functional cortical activity and visual-perceptual abilities in school-age children born at extremely low gestational age. *Pain* ; 154(10):1946–1952. [PubMed: 23711638].
- Runau RE, Whitfield MF, Petrie-Thomas J, et al 2009. Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18 months in preterm infants. *Pain* ; 143:138–146. [PubMed: 19307058]
- Vinall J, Miller SP, Synnes AR, Grunau RE 2013. Parent behaviors moderate the relationship between neonatal pain and internalizing behaviors at 18 months corrected age in children born very prematurely. *Pain* ; 154(9):1831–1839. [PubMed: 23748079]
- Ranger M, Synnes AR, Vinall J, Grunau RE 2013. Internalizing behaviours in very preterm school-age children are predicted by neonatal pain and morphine exposure. *Eur J Pain*. (doi: 10.1002/j. 1532-2149.2013.00431.x.)
- Anand KJ 2007. Pharmacological approaches to the management of pain in the neonatal intensive care unit. *J Perinatol* ; 27:S4–S11. [PubMed: 17453028]
- Durmeyer X, Vutskits L, Anand KJ, Rimensberger PC 2010. Use of analgesic and sedative drugs in the NICU: integrating clinical trials and laboratory data. *Pediatr Res*; 67(2):117–127. [PubMed:20091937]
- McPherson CC, Grunau RE 2014. Neonatal pain control and neurologic effects of anesthetics and sedatives in preterm infants. *Clin Perinatol* ; 41:209–227. [PubMed: 24524456]
- Marlow N 2014. Anesthesia and long-term outcomes after neonatal intensive care unit. *Paediatr Anaesth* ; 24:60–67. [PubMed: 24330445]
- Bellù R, de Waal KA, Zanini R 2008. Opioids for neonates receiving mechanical ventilation. *CochraneDatabase Syst Rev*; 1:CD004212. [PubMed: 18254040]
- Batton DG, Barrington KJ, Wallman C 2006. Prevention and management of pain in the neonate: an update. *Pediatrics*; 118:2231–41. [PubMed: 17079598]
- Pillai Riddell RR, Racine NM, Turcotte K, et al 2011. Non-pharmacological management of infant and young child procedural pain.

- Cochrane Database Syst Rev.; 5(10):CD006275. [PubMed:21975752]
- Stevens B, Yamada J, Lee GY, Ohlsson A 2013. Sucrose for analgesia in newborn infants undergoing painful procedures. Cochrane Database Syst Rev; 1:CD001069. [PubMed: 23440783]
- Taddio A, Yiu A, Smith RW, Katz J, McNair C, Shah V 2009. Variability in clinical practice guidelines for sweetening agents in newborn infants undergoing painful procedures. Clin J Pain; 25(2): 153–5. [PubMed: 19333162]
- Milgrom J, Newnham C, Anderson PJ, et al 2010. Early sensitivity training for parents of preterm infants: impact on the developing brain. Pediatr Res.; 67:330–335. [PubMed: 19952869]
- Brummelte S, Grunau RE, Zaidman-Zait A, Weinberg J, Nordstokke D, Cepeda IL 2011. Cortisol levels in relation to maternal interaction and child internalizing behavior in preterm and full-term children at 18 months corrected age. Dev Psychobiol ; 53(2):184–95. [PubMed: 21298633]