Are There Long-Term Consequences of Pain in Newborn or Very Young Infants?

Gayle Giboney Page, RN, DNSc, FAAN

GAYLE GIBONEY PAGE is an associate professor and the Independence Foundation Chair in Nursing Education in the School of Nursing at Johns Hopkins University in Baltimore, Maryland.

Abstract

Physiologic studies indicate that very early pain or stress experiences have more than immediate consequences for infants. Assessment and care of pain are complex subjects made even more complex and challenging when the individual experiencing pain is a very young infant. This review provides evidence that significant and long-lasting physiological consequences may follow painful insults in the very young, including changes in the central nervous system and changes in responsiveness of the neuroendocrine and immune systems to stress at maturity.

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Introduction

Pain is difficult to assess and even more challenging when its victims are very young or preverbal. This is especially true of newborn infants, either full or preterm. For years, health-care practitioners in the United States have cared for infants without viewing pain as one of the significant risks or disadvantages in making treatment decisions. This was not because anyone *wanted* to hurt babies. Superficial observations conceded that pain medications had some risks along with their advantages, and that infants seemed to forget pain anyway. If the patient never returns to complain about the pain later, how could it be very important? Now, as the knowledge base about infant development and human physiology is rapidly growing, serious flaws

in old assumptions emerge to challenge long-held beliefs about pain in infants. Recent physiologic studies increase the urgency for professionals to replace this old model of infant pain with one that recognizes its potential for negative and long-term impacts. The goal is to provide the healthiest outcome for infants; thus, health-care professionals, including perinatal nurses, need to develop a model of infant pain outcomes based on the best evidence. This is true for all infants and is especially true when caring for preterm human infants or sick newborns.

Premature human infants and sick newborns, given their typical experiences, are subjected to multiple procedures including heel lancing, intravenous catheter insertion, chest tube insertion, endotracheal tube suctioning, and surgery. Indeed, a longitudinal study showed that the youngest preterm neonates undergo an average of 750 procedures during their hospital stay (Porter, Wolf, & Miller, 1999). Premature infants in Canadian neonatal intensive care units (NICUs) were subjected to an average of two and up to eight painful procedures per day. For these infants, analgesic agents were provided in only 6.8% of all procedures (Johnston, Collinge, Henderson, & Anand, 1997). A recent cohort study showed that less than 10% of the sickest of NICU infants received opioids compared to 22–33% of those at lesser risk for neurologic impairment (Stevens et al., 2003). Growing evidence shows that early pain experiences in newborn infants may have long-term consequences and, yet, have only been minimally monitored in published studies.

In this literature review, evidence supporting the suggestion that early pain experiences have long-term sequelae is provided in two parts: the long-term perseverance of central nervous system changes following painful insults in the very young organism and, similarly, long-term changes in responsiveness of the neuroendocrine and immune systems to stress at maturity.

The Development of Pain Processing and the Neuronal Consequences of Tissue Injury

The Similarity of Rat Pups and Human Infants in the Maturity of Pain Pathways and Mechanisms

The development of pain-processing circuitry in the somatosensory nervous system continues beyond birth in both the human and the rat. For the purposes of this discussion, it is important to document that the development of the pain response follows a parallel trajectory in the human and the rat. The critical developmental points at which these two species achieve the same milestone both support this position of parallel developmental trajectories and serve to relate postconceptual age (PCA) in the human with postnatal age of the rat. (PCA is a term used after birth. Before birth, it is referred to as gestational age.) The cutaneous flexion reflex, evoked with repetitive nonpainful low-intensity stimuli to the foot, can be elicited in both premature and full-term neonates as well as in rat pups and has been suggested to reflect the excitability of the neonatal spinal cord. The flexor reflex threshold has been shown to increase with postnatal age in both species, which means it takes greater stimulation to elicit the reflex withdrawal response. As the reflex threshold increases, habituation to the reflex becomes more prominent (that is, the response to stimulation diminishes). The premature neonate habituates to such repetitive stimuli by 37–39 weeks PCA and the largest increase in the threshold (i.e., habituation) in the rat pup occurs during the second and third postnatal weeks (Andrews & Fitzgerald, 1994; Fitzgerald, Shaw, & MacIntosh, 1988). Researchers generally agree that the neurological maturity of pain pathways and mechanisms are similar between the rat pup at birth and the preterm human neonate of 23–24 weeks PCA (Anand, 2000; Porter & Grunau, 1999). Thus, results from studies of rat pups can be considered when exploring issues regarding the development of the somatosensory nervous system in human infants.

Long-Lasting Hypersensitivity to Pain from Early-Tissue Injury

Studies in pre-weanling rat pups have shown that several characteristics of the developing neuronal circuitry contribute to enhanced sensory and pain responsiveness in the very young rat. First, stimulation of touch-sensitive peripheral nerve fibers (A-fibers) evokes activity in the dorsal horn of the spinal cord. The dorsal horn is the area activated by pain-transmitting C-fibers in the mature rat and human. In rats, C-fiber stimulation (e.g., painful mechanical pressure) does not evoke dorsal horn activity until the tenth postnatal day

(Jennings & Fitzgerald, 1998). Second, the receptive field areas in the dorsal horn of the spinal cord that respond to cutaneous stimulation are relatively large at birth and decrease in size with age over the first three postnatal weeks (Fitzgerald, 1985). This phenomenon allows for stimulation of a relatively small area of the skin to evoke in the newborn a proportionately greater number of neurons in the spinal cord, amplifying the information that ultimately gets to the brain. Finally, a key descending pathway via which the brain can inhibit ascending pain input is nonfunctional at birth despite anatomical evidence of an intact pathway. Responses to descending stimulation begin to emerge during the second postnatal week and do not resemble those of the mature animal until postnatal day 19 (Fitzgerald & Koltzenburg, 1986). Taken together, these characteristics contribute to a processing of somatosensory information that is fundamentally different in the pre-weanling rat pups than that of the mature organism—a processing that is hypothesized to also influence the transmission of sensory input to the spinal cord in the human neonate (Fitzgerald & Jennings, 1999).

Injury in the rat pup has been shown to have profound effects on both peripheral and central neuronal circuits. For example, full-thickness skin wounding of the hind paw during the first 21 postnatal days was shown to result in local hyperinnervation associated with healing of the wound such that the number and density of cutaneous axons was significantly increased, remarkably so when pups were wounded before postnatal day 7. At three weeks after pups were wounded on postnatal day 0, the mechanical flexion reflex threshold remained markedly lower compared to nonwounded animals, indicating *long-lasting local hypersensitivity* to pain (Reynolds & Fitzgerald, 1995). Recently, plantar skin wounding on the day of birth was shown to enlarge the organization of receptive fields in the dorsal horn assessed in the young adult rat, which is consistent with observations of long-lasting behavioral indicators of hypersensitivity to pain (Torsney & Fitzgerald, 2003).

Increased Pain Sensitivity from Early Human Pain Experiences

In humans, the following evidence suggests that tissue injury during the early neonatal period may result in similar enhancement of somatosensory responses as has been observed in rats. In a longitudinal study of neonates born at 27–32 weeks PCA, when heel lancing was restricted to one side, periodic flexor reflex threshold testing showed a consistently *reduced* threshold for the affected heel compared to the noninjured heel, indicating an increased pain sensitivity on the side of heel lancing. Compared to untreated and placebo controls, when a group of infants was treated regularly with a topical anesthetic beginning three days after heel lancing was initiated, flexor reflex thresholds between the injured and noninjured side became equivalent (Fitzgerald, Millard, & MacIntosh, 1989). These findings show that the human neonate is capable of mounting an inflammatory response with persisting hyperalgesia, or increased sensitivity to pain, due to early painful experiences—a response that can be ameliorated by local anesthetic application.

Additional studies in humans have supported the suggestion that tissue injury at a young age may have long-lasting somatosensory sequelae. First, Andrews and Fitzgerald (1999) showed that the indicator of the excitability of the neonatal spinal cord—a mechanically evoked flexion reflex threshold to stimuli applied to the foot and leg—increased with age in normal comparison infants of PCA 28–42 weeks. However, similar infants with a substantial leg injury did not exhibit the normal age-related increase in threshold, even when the noninjured leg was tested. This absent development of normally increasing thresholds contralateral to the injury reflects substantial "secondary" changes in the spinal cord itself and not merely to the injured leg. In a related study, infants born with unilateral hydronephrosis were recently shown to exhibit increased abdominal sensitivity on the affected side, as well as evidence supporting referred hypersensitivity to the contralateral side. Additionally, the normal increase in abdominal reflex threshold observed in comparison infants was not observed in infants with unilateral hydronephrosis, again suggesting spinal cord changes as opposed to a local impact (Andrews, Desai, Dhillon, Wilcox, & Fitzgerald, 2002).

Finally, studies reveal that lasting changes in pain sensitivity with the early experience of pain have been found in full-term infants as well. Using a prospective cohort design in males, one study found that facial pain-score coding from videotape recordings at

four- or six-month routine vaccination was related to circumcision status as well as pain treatment for the procedure (Taddio, Katz, Ilersich, & Koren, 1997). In particular, a significant linear trend of increasing facial pain scores during immunization emerged from uncircumcised (lowest) to circumcised infants with topical lidocaine-prilocaine cream (mid) to those who were circumcised with placebo (highest). Thus, research on rat pups, preterm human infants, and full-term infants all show that the introduction of early pain has long-term effects on the development of pain processing.

The Impact of Early-Stress Experiences on Neuroendocrine and Immune Function at Maturity

Immune function is another area impacted by early experiences with pain or stress and consistently shown in animal studies. The following studies of the impact of neonatal stressors upon neuroendocrine and immune function in the mature rat tend to show that, compared to animals remaining unperturbed throughout the neonatal period, neonatally stressed animals exhibit both decreased neuroendocrine and immune function at baseline and compromised function following stress at maturity. This literature has historically focused upon neonatal stressors such as maternal separation or deprivation, or endotoxin administration. More recently, two studies of early pain have emerged.

Influences of Maternal Separation as the Stressor in Rat Studies

The impact of maternal separation or deprivation on stress reactivity in the mature animal appears to be bimodal. This means an over- or under-response to stress can occur. Separation from the dam for short periods of handling are associated with an "inoculating" effect whereby hypothalamic-pituitary-adrenal (HPA) axis responses to stress are somewhat blunted and the return to basal levels of corticosterone is more rapid compared to animals that were not perturbed prior to weaning (Anisman, Zaharia, Meaney, & Merali, 1998). In support of this phenomenon with regard to immune function, study results showed that neonatal mice exposed to clean bedding without the mother for 15 minutes per day on postnatal days 3–14 exhibited a protective, increased NK-cell activity and T-cell proliferation in response to two different mitogens, α CD3 and phytohemagglutinin (Neveu, Deleplanque, Puglisi-Allegra, D'Amato, & Cabib, 1994). On the other hand, early extended maternal deprivation of more than 2–3 hours per day is associated with increased HPA axis responsiveness in the adult (Anisman et al., 1998; Hodgson, Rosengren, & Walker, 2000). With regard to immune function, withdrawal of the mother from the cage for 2 hours per day on either postnatal days 15, 18, and 21 or days 0–28 resulted in a significant suppression of the plaque-forming cell response to sheep red blood cells, a test of the animals' ability to form antibodies to a foreign antigen (von Höersten, Dimitrijevic, Markovic, & Jankovic, 1993). Compared to undisturbed pups, rat pups who had been separated from their mother 2 hours per day for the first 21 days of life exhibited significantly greater susceptibility to the metastasis of MADB106 tumor cells injected at 60 days of age (Hodgson et al., 2000). Finally, early weaning at postnatal day 15, rather than the usual practice of 22 days, was associated with profound lymphopenia; however, when the reduced body weight was accounted for statistically, this difference became insignificant. On the other hand, accounting for reduced body weight did not affect the observed reduction in the lymphocyte proliferative response to phytohemagglutinin stimulation (Ackerman et al., 1988).

Influences of Endotoxin as the Stressor in Rat Studies

Injecting rat pups with endotoxin—the components of microbial structures that are typically heat-killed—results in acute-phase and inflammatory responses characterized by massive inflammatory cytokine release with generalized immune suppression (Janeway, Travers, Walport, & Capra, 1999) and HPA axis activation (Shanks, McCormick, & Meaney, 1994). Endotoxin injection on as few as two occasions in the first week of life has been shown to exacerbate responses to stress much later in the mature animal, including HPA axis activation indicators (Hodgson et al., 2000; Shanks, Larocque, & Meaney, 1995), stress-induced suppression of lymphocyte proliferative responses (Shanks et al., 2000), and increased susceptibility to the metastasis of NK-sensitive MADB106

tumor cells (Hodgson et al., 2000). Neonatal endotoxin injection in rats has also been shown to result in delayed wound healing in the mature animal (Hodgson et al., 2000), which reflects the animals' inability to mount an inflammatory response (Padgett, Marucha, & Sheridan, 1998). The results are consistent with the findings of Shanks and colleagues (2000) that neonatal endotoxin-treated animals did not exhibit the expected increase in paw volume following induction of adjuvant arthritis.

Influence of Pain as the Stressor in Rat Studies

From the above review, we learn that the animal literature largely supports the hypothesis that neonatal *stressful experiences* affect mature biobehavioral responses to stress; however, studies specifically addressing neonatal *pain* and the immune system are rare. In a notable, recently published study, neonatal rats underwent either a cotton swab rub (no pain) or needle prick (painful) on a separate paw, two or four times per day at hourly intervals for the first 8 days of life (Anand, Coskun, Thrivikraman, Nemeroff, & Plotsky, 1999). Behavioral testing compared only the four-times-per-day groups and showed that, compared to the paw-rub group, the needle-prick group later exhibited increased pain sensitivity evidenced by shorter baseline hot-plate latencies (52° C) in preadolescence, but not at adulthood. (Hot-plate latency is the time it takes for the rat to exhibit the characteristic pain response, hind paw lick, to being placed on the heated plate, at which time the animal is removed from the plate.) When the animals reached adulthood, compared to the paw-rub group, the needle-prick group exhibited (1) greater anxiety assessed as significantly increased time spent in a dark tube placed in a lit "open field"; (2) a significant alcohol preference; and (3) social hypervigilance manifesting as prolonged chemosensory memory of a novel juvenile rat. There was consistency among all three tests as being indicative of greater levels of anxiety in the animals that underwent paw needle-prick early in life compared to those undergoing paw touch. For example, animals injected with valium are more likely to enter the lit area compared to rats not receiving valium (Aburawi, Elhwuegi, Ahmed, Saad, & Attia 2003). Additionally, compared to paw-rub animals, adult animals that underwent a neonatal needle prick manifested significantly fewer Fos-immunoreactive cells in the somatosensory cortex at 30 minutes after hot-plate exposure. Given that Fos expression is a transient and early gene that is expressed in response to pain or stress, Anand and colleagues (1999) suggested that the relatively greater neuronal activation observed in the paw-rub group was consistent with greater cortical stress responsiveness. The greater neuronal activation was also evidenced by the escape behavior exhibited by the paw-rub rats versus the in-place freezing behavior that was exhibited by the needle-prick rats during the hot-plate testing (Anand et al., 1999). This paradigm was designed to approximate the longest period for which extremely low-birth-weight (ELBW) human neonates often stay in the NICU (Lidow, 2002).

Maternal Touch and Grooming as a Stress Indicator

A similar needle-prick paradigm of once-daily paw pricks for postnatal days 2–14 showed that, compared to pricked pups, unhandled pups exhibited higher adrenocorticotropic hormone levels in response to a mild stressor at 15 or 20 days of age. Additionally, an observation of increased maternal grooming in the pricked pups, compared to paw-rubbed animals, may support evidence that mother-pup interaction acts as a buffer to early stress experiences (Walker, Kudreikis, Sherrard, & Johnston, 2003). Indeed, mother-pup interactions, particularly maternal grooming and anogenital licking of the pup, have been shown to reduce later HPA axis-mediated responses to stress in the mature rat as well as reduced fearfulness in a novel environment (Caldji et al., 1998; Francis, Diorio, Liu, & Meaney, 1999; Liu et al., 1997). Thus, increasing evidence shows that maternal factors play a key role in mediating the impact of the environment on the physiology of the developing rat neonate (Shanks & Lightman, 2001).

Long-Term Impact of Early Stress on Humans

Possible long-term sequelae of early intensive care with implications of associated pain experiences are markedly less well studied. From the previously reviewed literature, we can assume that preterm infants, as a group, experience far more painful procedures than full-term infants and that the lowest-weight preterms

experience the most painful procedures. A rather large amount of literature, both retrospective and prospective, employs statistical techniques to characterize the growth and development of premature human infants through early childhood; however, virtually no analysis exists related to painful experiences per se. On the other hand, neurologic, developmental, and neurosensory morbidities such as increased pain sensitivity and temperament have been shown to increase as birth weight decreases (Grunau, 2002; Vohr et al., 2000; Zeltzer, Bursch, & Walco, 1997). Given that findings from Porter and Grunau (1999) indicate that the incidence of invasive procedures increases as birth weight decreases, the notion that painful experiences play a role might be reasonable, especially in light of the above-mentioned neurosensory findings. These findings should be addressed in studies of infant morbidity.

Thus far, specific efforts to explore the issue of early pain and its consequences have provided only hints, as shown in several recent comparison studies of children who were of normal birth weight versus ELBW. Grunau and colleagues recorded findings worthy of notice. In one study, toddlers who were former ELBW infants were rated by their parents as expressing significantly lower pain sensitivity (Grunau, Whitfield, & Petrie, 1994). In another study, children at 4 1/2 years of age who were former ELBW infants exhibited a higher incidence of somatization scores above the clinical cutoff—9 of 36 versus 0 of 36 full-term infants (Grunau, Whitfield, Petrie, & Fryer, 1994). By the time the children reached 8–10 years of age, few differences were discovered with regard to perceptions about pain; however, unlike the normal birth-weight group, the ELBW group rated medical pain intensity significantly greater than psychosocial pain (Grunau, Whitfield, & Petrie, 1998). Saigal and colleagues (1996) found that adolescents who were ELBW indicated greater morbidity in rating their health-related quality of life versus a comparison group of adolescents—although it was noted that a large majority of the ELBW group indicated their health-related quality of life was quite satisfactory. Finally, a provocative prospective case control study in Sweden estimated that multiple birth trauma increased the relative risk for adult violent suicide from 1 to 4.9 in men versus 1.04 in women (Jacobson & Bygdeman, 1998). Additionally, the researchers found that the provision of opioids to the mother at the time of delivery lowered the suicide risk to 0.69 in both sexes (Jacobson & Bygdeman, 1998).

The attribution of pain vulnerability or psychologic sequelae to early-pain experiences is undeniably a complex issue. Examples of additional foci that warrant consideration and research with regard to the pain-vulnerable child include such issues as the ability to regulate attention and arousal related to the anxiety associated with impending painful events, temperament, memory of past events, and responses of others in the pain situation (Zeltzer et al., 1997).

Conclusion

Physiologic studies in animals indicate that very early pain experiences may have more than immediate consequences in infancy. Ongoing lowered pain thresholds in the injured area indicate that changes occur in the still-developing spinal cord. Early stress may lead to a reduced immune system response, resulting in consequences such as delayed wound healing and potentially an increased susceptibility to infection. Increased pain sensitivity, decreased immune system functioning, increased avoidance behavior, and social hypervigilance are all possible outcomes of untreated pain in early infancy.

Although an individual may not preserve a conscious memory of an early painful event, it is recorded elsewhere in the body, as evidenced by the previously presented long-term outcomes. Multiple procedures in the preterm and low- to extremely low-birth-weight infant, as well as "routine" newborn medical procedures (from heel sticks to circumcision), may alter infant development. The implication is that infant pain should be avoided when possible and, when necessary, assessed and treated at least as diligently as adult pain. Maternal touch should be facilitated, especially in infants subjected to painful procedures for any ameliorating effects.

Implications for Childbirth Educators

What can a childbirth educator offer to parents whose infants may or must undergo painful procedures? First, parents—as well as caregivers—need to recognize that pain must be added to the list of risks when deciding whether to provide a treatment or consent to a procedure

in an infant. This consideration has not been a part of the traditional decision-making model for most practitioners. Also, it takes time to implement changes in thinking. Knowledge is the first step in making that change.

As they interact with community nurses and physicians, informed childbirth educators should advocate for infants regarding minimizing pain experiences and increasing comfort measures. Childbirth educators also have a primary responsibility and an opportunity to share this knowledge with new and expectant parents. Parents need to know that what would be painful and detrimental to them would also be painful and detrimental to their infant, perhaps even more so. Second, parents have support in research to insist that caregivers treat their infant's pain just as they would want their own pain treated. Finally, these physiologic studies reinforce the strong benefits of infant soothing and human contact to help the infant cope with stressors. Pain is a major stressor. The prolonged, intimate contact that is part of the normal human mother-infant experience—with its skin-to-skin contact, motion, and active touch—is a widely practiced treatment for an infant who is uncomfortable or has suffered trauma and pain, whether at birth, in the hospital nursery, or anywhere else. Without waiting for the research to grow in this area, parents and other care providers should maximize their use of these techniques with full-term and preterm infants. A knowledgeable professional and a knowledgeable parent both have a role in the prevention and treatment of the negative consequences of infant pain.

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