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How Long Does Incisional Pain Last: Early Life Vulnerability Could Make It Last a Lifetime

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The existence of critical periods of development is an established concept. The vulnerability to potentially adverse effects from "exposure" to certain drugs and stresses at specific times during development is concerning. Recent effort has focused on the impact of exposure to anesthetics during critical periods of development and the detrimental effects on the nervous system.[1] However, this month in *Anesthesiology* two research articles by Walker and colleagues highlight changes in the nervous system from incisional surgery at a critical or vulnerable period of development. [2,3] These effects are independent of the anesthetic exposure and highlight the reemerging concept of surgery and pain as an "exposure" that results in long-term changes in the developing nervous system, and returns us to the role anesthesia and analgesia play in modulating and minimizing the long-term impact of surgery and inflammation.

The authors have focused on two components of noxious input early in life, the potential impact on the neuroinflammatory responses induced by glia in the central nervous system, and alterations in descending spinal cord input. Both studies confirm that incoming nociceptive input from the periphery is the key driver, affecting both the spinal cord and also higher centers, in this case the rostroventral medulla (RVM) which provides important descending input for modulation of sensory neurotransmission in the spinal cord. This is demonstrated by the fact that peripheral nerve blockade reduces or eliminates changes in these parts of the nervous system following incisional surgery. This may have implications for treatment regimens that are effective given age-specific goals and concerns. Nerve blockade also confirms that the changes are independent of systemic stress responses or maternal separation and directly related to neuronal input. Additionally, the finding that altered responses to nociceptive input later in life are not somatotopically restricted to the previously injured location suggests a more generalized response to previous injury.

The simplest interpretation of these two studies taken together is that early surgery alters future responses by changing the balance of descending input from the RVM and increasing the central neuroinflammatory response to future injury. More complex, however, are the implications of these alterations, especially neural immune interactions in higher order brain regions and associated processes when surgery occurs at critical periods. Changes in the

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RVM suggest that early nociceptive input may affect development beyond the spinal cord and brainstem, since the RVM connects to more rostral centers, and nociceptive inputs from the spinal cord have connections to higher cortical and subcortical areas as well. Balanced neuronal excitatory and inhibitory input to the nervous system is required for normal maturation of nociceptive circuits in the spinal cord and connections in the brain; synaptic winnowing and synaptic strengthening occur simultaneously and in response to increases and decreases in activity.[4] These studies support the concerning possibility that peripheral nociceptive inputs at critical periods may enhance synaptic strengthening inappropriately or winnow connections that help develop integrated forebrain circuits. This may in turn impact pain processing and environmental interactions later in life and result in altered development of higher order brain circuits and their function. Thus, the possibility exists for potential long-term and evolving behavioral effects as a direct result of inadequate anesthesia and analgesia in the young.

Implications for the “priming” that occurs in response to this early exposure to noxious stimulation is concerning. The enhanced activation of glial cells in the spinal cord after the second, or reexposure to, surgical incision could reflect a process akin to immunologic memory leading to the “primed” glia response. The reexposure could also reflect a more profound response to an abnormal pattern of neuronal activation from the periphery resulting from prior alterations in neuronal sensibility or transmission patterns. Neuroglia activation from a second surgery would be particularly concerning if it is widespread and not somatotopically restricted, since other aspects of inflammation in the central nervous system could possibly result in worsening neurologic dysfunction from an insult or pain.

I often hear the question in regards to basic research, “What does that mean, really?” Certainly there are limitations to animal studies. Ideally, we would collect life-long data in all patients, but this is not reality—maybe someday! In the meantime the weakness of the studies remains that we are extrapolating developmental effects in rats to humans. Despite this shortcoming, these studies are valuable and important. Their strength resides in the ability to probe complex interactions and the impact of pain and injury in the neonatal period. The animal studies permit exploration of immune and neural feedback circuits that may occur in humans. The delicate balance of factors and the long time horizon makes these studies time consuming and difficult, or may be impossible in humans with current tools and limited resources. Thus, these studies contribute significantly by helping to identify patterns of injury and associated issues in small studies that permit isolating effects, exploring mechanisms, and evaluating their potential long-term implications. This may result in accelerating the development of strategies to improve safety, reduce harm, and permit alternative and more rapid models for their evaluation. This highlights and emphasizes the importance of basic science research in guiding and informing clinical concerns and potential interventions.

This work does raise many questions:

1. What are the implications for children having surgery? Do genetics play a role? What is the role of different anesthetics during the most profound nociceptive barrage? Should nerve block be used? How long?

2. What is the effect of postoperative analgesic regimens? Is an adequate analgesic regimen enough to prevent the effects of incision? What is the role of nonsteroidal antiinflammatory drugs or narcotics?

3. Does reduced sensory capability affect performance in fine functioning motor and sensory skills? Or is it protective as an adaptive response?

4. Does the increased inflammatory cell activation from reexposure occur only in the centrla nervous system, or does it occur elsewhere resulting in reduced recovery and/or prolonged pain? Or does it actually accelerate healing later?

5. Is it previous surgery and neural input alone, or does any type of inflammatory response produce similar changes, globally and more specifically in the spinal cord and peripheral neurons? Do the changes in neuroinflammatory responses result in changes in susceptibility and risk from large inflammatory response injuries such as trauma and sepsis in later life?

As perioperative physicians, the answers to these questions are important for further refinement of age-dependent and specific care for children during critical periods of development. Although the articles by Walker and colleagues remind us to consider long-term ramifications of perioperative care, the approach and therapies to best manage children in early development requiring surgery and anesthesia are not clear. These articles serve to remind us that we have many knowledge gaps and much to learn about the long-term implications of the perioperative period, particularly in children during periods of vulnerability. Additionally, the temporal relationship of surgery and anesthesia to long-term effects makes establishing connections and defining patterns extraordinarily difficult and emphasizes the use of models to probe concerns, injury patterns, and even test therapeutic interventions. Ultimately, however, the validity of these ideas and concepts will need to be established in humans, and care guidelines for the perioperative period generated that are developmentally targeted to minimize the impact of early life surgery and anesthesia in later life. Although costly and time consuming, more long-term human studies need to be funded to establish and reduce the long term impact of surgery in children during critical periods.

The care of patients involves not only considerations of past history and current status, but greater understanding of interactions short and long-term as an integral factor in optimizing outcomes; this is a different way of thinking and an important concept emerging in perioperative care. The value and importance of this concept regarding surgery early in life cannot be underestimated as the children are the future. As anesthesiologists we routinely take care of children and adults and rarely consider the long-term impact of our care and interventions. However, as the perioperative environment evolves, our jobs as perioperative physicians likely are getting more difficult as the nuances of small changes in management may result in large changes in outcomes later in life. Nowhere is this emerging more clearly than in the management of small children in the perioperative period. Basic science guidance has been and will likely continue to be the driver, but clinical studies will hold the definitive answers.

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References

1. Lin EP, Soriano SG, Loepke AW. Anesthetic neurotoxicity. Anesthesiol Clin. 2014; 32:133–155. [PubMed: 24491654]
2. Walker SM, Fitzgerald M, Hathway GJ. Surgical injury in the neonatal rat alters the adult pattern of descending modulation from the rostroventral medulla. Anesthesiology. 2015; XXX:XXX–XXX.
3. Schwaller F, Beggs S, Walker SM. Targeting p38 mitogen-activated protein kinase to reduce the impact of neonatal microglial priming on incision-induced hyperalgesia in the adult rat. Anesthesiology. 2015; XXX:XXX–XXXX.
4. Holtmaat A, Svoboda K. Experience-dependent structural synaptic plasticity in the mammalian brain. Nat Rev Neurosci. 2009; 10:647–658. [PubMed: 19693029]