Pain Begets Pain

Predictors of Long-term Phantom Limb Pain and Post-thoracotomy Pain

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Dworkin has written a timely Focus article in which he discusses factors associated with the transition of acute pain to chronic pain. Perhaps the most interesting and important argument he makes is that the severity of acute pain predicts chronic pain. In light of the bewildering number of factors associated with chronic pain, the multitude of chronic pain disorders in existence, the numerous peripheral and central nervous system mechanisms known to contribute to pain, and the disparate inclusion/exclusion criteria used in studies of chronic pain, it is somewhat surprising that severity of acute pain emerges as a risk factor for chronic pain. Nevertheless, data are available to support this view, but controlled prospective studies are needed to confirm and corroborate this position. If it should turn out that severity of acute pain does in fact predict the development of chronic pain, then we must grapple with the following questions: What is it about severe pain that is linked to the development of long-term pain? Is it something about the pain per se or the individuals who report severe pain? Will aggressive management of severe acute pain alter the course and lead to a decreased incidence of long-term pain problems? I limit my commentary to the phantom limb pain and post-thoracotomy pain literature. I consider the evidence for and against Dworkin's argument that the severity of acute pain is a risk factor for these chronic pain conditions.

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PHANTOM LIMB PAIN

Although there is a widespread belief in the position put forth by Dworkin, there are surprisingly few prospective data to support the position. We need to examine the role of at least three factors and possibly their interaction in the development of long-term pain after amputation: (1) preamputation pain; (2) noxious intraoperative inputs brought about by the cutting of skin, muscle, nerve, and bone; and (3) acute postoperative pain (including inflammatory pain).

Relationship Between Preamputation Pain and Phantom Limb Pain

What is the role of preamputation pain in the subsequent development of phantom limb pain? There are two claims: One is that pain occurs more frequently in patients who experienced pain in the limb before amputation than in patients who were pain-free. The second claim is that there is a similarity (in quality, location, intensity) between the pain experienced before amputation and the phantom limb pain (e.g., the pain memories reported by Katz and Melzack [16] and others). It should be noted that a statistical analysis that tests whether phantom pain occurs more frequently in patients who experienced pain before amputation than in those who did not does not necessarily address the issue of the similarity of pain before and after amputation. Unless backed up with additional information on the nature of the similarities between the preamputation and phantom limb pains, the association between pains may have nothing at all to do with amputation. As certain individuals suffer more pain than other individuals, it would not be surprising to find that this is true both before and after amputation (or at any other two points in time).

Jensen et al. [11] carried out the only prospective, long-term study designed to examine the relationship

between preamputation pain and the subsequent development and course of phantom limb pain. Information was obtained regarding the location and character of pain experienced the day before amputation and, again, with respect to phantom limb pain, 8 days, 6 months, and 2 years after amputation. Preamputation pain and phantom limb pain were similar in both location and quality in 36% of patients 8 days after amputation and had decreased to 10% at the 6-month and 2-year follow-up visits. In addition, the presence of pain on the day before amputation and the duration of preamputation pain predicted phantom limb pain at the 6-month follow-up visit but not 2 years later: the incidence of phantom limb pain was significantly higher in patients who reported preamputation pain that had lasted more than 1 month when compared with those who reported preamputation pain that lasted less than 1 month.

There are two implications to the finding that the incidence of phantom limb pain 6 months, but not 2 years, after amputation was significantly greater in amputees who had long- as opposed to short-lasting preamputation pain. Either some of the amputees who had had longstanding preamputation pain and phantom limb pain at the 6-month assessment were no longer in pain at the 2-year follow-up visit, or some amputees who had had short-lasting preamputation pain and no phantom limb pain at 6 months developed phantom pain by the 2-year follow-up visit. An examination of the data reveals that neither of these possibilities occurred. Seventeen amputees died between the 6-month and 2-year follow-up visits, thus reducing the size of the sample, but of the patients who had had longstanding preamputation pain, the proportions with and without phantom limb pain remained virtually unchanged at the two assessments. Similarly, there is no evidence that the patients who had had preamputation pain of short duration and no phantom limb pain at the 6-month assessment subsequently developed it. In fact just the opposite occurred: at the 2-year follow-up visit, there were proportionally fewer amputees with phantom limb pain. As there was little change over time in the distribution of phantom limb pain within short- and long-lasting preamputation pain categories, it is probably best to interpret the lack of a significant relationship between the duration of preamputation pain and the persistence of late phantom limb pain as a type II error, resulting from a loss of statistical power due to the reduced sample size at the 2-year follow-up visit. This suggests that 2 years after amputation, the effect of long-standing preamputation pain can still be detected as an increased incidence of phantom limb pain when compared with patients who had preamputation pain of shorter duration. This is an important conclusion for it links the report of longstanding preamputation pain to long-lasting phantom limb pain and points to the potential importance of maintaining patients free from pain for as long as possible before amputation.

Effects of Reducing Preoperative Pain, Blocking Noxious Intraoperative Inputs, and/or Reducing Acute Postoperative Pain on the Development of Phantom Limb Pain

Dworkin includes a brief discussion of implications for the prevention of chronic pain. He alludes to the literature on preemptive analgesia and the role of noxious pre- and intraoperative stimuli in the development of prolonged pain. In this section, I expand on Dworkin's argument because of the substantial potential preemptive and other preventive approaches have for reducing the incidence and intensity of long-term phantom limb pain. Although short-term preemptive analgesic effects following major surgery have been reported for lateral thoracotomy [15], laparoscopic cholecystectomy [20,21], lower abdominal surgery [12], and abdominal hysterectomy [13,22], the long-term benefits associated with blocking noxious inputs before, during, and/or after limb amputation are truly remarkable [1,10,23] notwithstanding the methodologic problems associated with these studies.

Bach et al. [1] found that 3 days of continuous epidural morphine plus bupivacaine administered prior to amputation reduced the incidence of phantom limb pain 6 months later compared with a control group that did not receive an epidural before amputation. Jahangiri et al. [10] compared a standard general anesthetic for amputation plus on-demand opioids for postoperative analgesia with a continuous infusion of epidural diamorphine, clonidine, and bupivacaine beginning 24 to 48 hours before amputation and continuing for a period of 3 days after amputation. The proportion of patients with severe phantom limb pain (≥ 3 on a visual analog scale of 1–10) was significantly lower in the epidural group at 7 days, 6 months, and 1 year after amputation. Schug et al. [23] reported a three-group study comparing a standard general anesthetic for amputation plus on-demand opioids for postoperative analgesia (group 1) with a continuous infusion of epidural bupivacaine and fentanyl beginning either 24 hours before (group 2) or immediately before (group 3) amputation and continuing for at least 48 hours after surgery. One-year follow-up data showed a significantly reduced incidence of phantom limb pain among patients provided the pre-, intra-, and postoperative epidural infusion (group 2) relative to those who received the general anesthesia plus systemic opioids (group 1). Two retrospective, studies [8,9] examined the effects of a 3–7-day continuous infusion of a local anesthetic into the sciatic or posterior tibal

nerve sheath after the nerves had been ligated and transected. Patients were assessed for phantom limb pain between 6 months and 1 year after amputation. The number of patients reporting phantom limb pain at follow-up evaluation was significantly less than in a control group in one study [9] but not in the other [8].

The studies by Bach et al. [1] and Schug et al. [23] evaluated the effect of (eliminating) preamputation pain on the subsequent development of phantom limb pain 6 months to 1 year later. Despite serious threats to internal and external validity, the studies by Fisher and Meller [9] and Elizaga et al. [8] are interesting because they evaluate the effects of blocking only postoperative inputs (i.e., in most cases preamputation pain was not relieved and intraoperative trauma was not blocked). The studies by Jahangiri et al. [10] and Schug et al. [23] were geared toward eliminating noxious inputs before, during, and after amputation. Taken together, the results of these studies suggest that preamputation pain and postoperative inputs each appear to contribute separately to phantom limb pain. The combined effects of noxious pre-, intra-, and postoperative input may increase the probability that long-term phantom limb pain develops.

The prospective intervention studies [1,10,23] provide some of the strongest evidence supporting a link between acute injury and the development of long-term phantom limb. Continuous epidural anesthesia and analgesia beginning before and continuing for several days after amputation appears to confer the most protection from the development of long-term phantom limb pain. As noted above, a number of methodologic problems limit the validity of these studies (e.g., small sample sizes, nonrandom assignment of patients to treatment, nonblinded treatment and pain assessment, insufficient details about pain assessment). Further research is required to isolate the relevant factors and their roles in determining pain at various points after amputation.

Phantom Limb Pain in Children and Adolescents: An Unknown Entity

The problem of phantom limb pain among children and adolescents has not received the clinical and research attention it deserves. To date, not one prospective study has been conducted even though retrospective studies indicate that approximately 7 years after amputation performed in childhood or adolescence, 70–75% of individuals continue to experience phantom limb pain [2]. A more recent survey of 24 individuals who underwent amputation in childhood or adolescence found a prevalence rate of 92% for phantom pain, with the pain persisting for months to years [17]. Biomedical risk factors for long-term phantom limb pain in pediatric amputees include cancer-related amputation and chemotherapy [24], but these findings must be confirmed in a prospective study.

Consistent with the literature from the adult amputee population it has been reported that phantom limb pain is more common if the child suffered preamputation pain [18]; however, not one prospective study has been carried to support these claims. We do not know the extent to which preoperative pain, noxious events during surgical amputation, and/or acute postoperative pain contribute to phantom limb pain in children.

ACUTE POSTOPERATIVE PAIN PREDICTS LONG-TERM CHEST WALL PAIN

Dworkin recommends a prospective, longitudinal research strategy that follows individuals at high risk for developing chronic pain (e.g., those undergoing amputation, those with acute herpes zoster). This strategy maximizes information yield while minimizing sample size. In addition to amputation, another surgical procedure that results in a high prevalence rate of long-term pain is a lateral thoracotomy incision for chest surgery [4,14]. A recent prospective study of 30 patients found that 52% reported daily or weekly pain of moderate intensity 1.5 years after lateral thoracotomy [14]. An examination of pre-, intra-, and postoperative factors showed that early postoperative pain was the only significant predictor of long-term pain. Pain intensity 24 hours after surgery was significantly greater among patients who developed long-term pain compared with pain-free patients. Cumulative morphine consumption was virtually identical for the two groups. This indicates that the intergroup differences in pain intensity were not mediated by postoperative analgesic usage. It also raises the possibility that compared with patients who were pain-free 1.5 years after surgery, those who developed long-term pain may not have been as responsive to an equal dose of morphine in the early postoperative period. Pre- and postoperative measures of anxiety and depression symptoms were comparable for the two groups, suggesting that psychological factors did not differentially influence the experience or reporting of pain. Finally, preoperative and postoperative pain thresholds applied to a rib contralateral to the incision did not differ significantly for patients who later developed long-term pain compared with those who were pain-free 1.5 years later. This latter finding is particularly important because it strongly suggests that the differences in acute postoperative pain intensity were not simply due to a response bias among patients with long-term pain to report noxious stimulation as more painful (as pain thresholds to pressure were similar at a time when postoperative pain

intensity differed). Would aggressive management of early postoperative pain have reduced the incidence of long-term post-thoracotomy pain? Would combining morphine with a low-dose continuous infusion of the *N*-methyl-D-aspartic acid channel blocker ketamine have altered the course of acute and long-term pain? We do not have answers to these questions but they represent logical first steps toward identifying the mechanisms responsible for the transition of acute, physiologic pain to chronic, pathologic pain.

HERITABILITY OF PAIN

Dworkin's model does not address the issue raised above of whether it is pain severity per se or something about the people in pain that links acute pain to the development of chronic pain. This is an important distinction because it has implications for treatment. Recent studies of the heritability of pain raise the possibility that genetics may play a role in the transition of acute to chronic pain [6,7,19]. Animal experiments carried out by Devor and Raber [7] using the autotomy model are pertinent to this issue.

In the autotomy model, the sciatic and saphenous nerves of the rat are transected at midthigh level, resulting in complete anesthesia and loss of motor function in the peripheral territories subserved by these nerves. Within 3 weeks of nerve sections, rats begin to bite and scratch the distal portions of the insensitive paw to the point of amputation. It is well established that autotomy is a response to pain or dysesthesias referred to the anesthetic limb and, therefore, represents an animal model of phantom limb pain [3,5]. As the nerve sections produce a deafferentation of the entire hindpaw, it is inferred that any pain or dysesthesias experienced in the denervated territory must be phantom pain.

Devor and Raber [7] developed two lines of rats by interbreeding those that exhibited high levels of autotomy and interbreeding those that showed low levels of autotomy. Offspring that showed high levels of autotomy were interbred as were those that showed low levels of autotomy. Interbreeding by selecting for high- or low-autotomy behavior was carried out for 13–15 generations. By the third generation, high- and low-autotomy rats could be distinguished by level of autotomy. By the eleventh generation the incidence of autotomy approached 90% among the high-autotomy line and was approximately 10% among the low-autotomy line. In addition, the kinetics of the self-mutilative behavior were altered in the high-autotomy line so that successive generations showed autotomy onset as early as the first week. Twelfth-generation high-autotomy rats showed significantly greater sensitivity on sensory and thermal testing than low-autotomy rats. Based on the pattern of autotomy among hybrid rats and backcrossed hybrids, the authors suggested that the mode of inheritance of the autotomy trait is through a single autosomal recessive gene. The strong genetic component associated with the autotomy trait raises the possibility that among patients, some may inherit a predisposition to develop chronic neuropathic pain after amputation.

CONCLUSIONS

Many aspects of Dworkin's model are testable. In fact, the hypothesis that the severity of acute pain is a risk factor for the development of chronic pain is already supported by empirical evidence. This has been demonstrated prospectively for preamputation pain and for acute postoperative pain after amputation and thoracic surgery. The relative contribution of preamputation pain, intraoperative trauma, and postoperative injury and inflammation to the development of phantom limb pain remains to be determined. In this regard, randomized, double-blind, controlled trials of preemptive analgesia and other preventive approaches using large sample sizes and reliable and valid pain assessments are required to firmly establish the relationship between acute pain and the subsequent development of phantom limb pain. Mechanisms underlying the transition of severe acute pain to chronic neuropathic pain remain to be determined.

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