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Persistent Postsurgical Pain

The Path Forward through Better Design of Clinical Studies

CHRONIC pain continues to be a major humanitarian and socioeconomic burden with slow progress in the development of new preventive and therapeutic options. Persistent postsurgical pain (PPP) is a well-known and common clinical entity with a reported incidence between 5 and 50% of patients after various common operations.[1,2] PPP has received increased interest during the past 10–15 yr. These patients can be studied before injury is inflicted, and thus, PPP provides a special opportunity to understand pathogenic mechanisms for developing a chronic pain state or the transition from an acute to a chronic pain state.

What have we learned from clinical trials regarding pathogenic mechanisms of PPP and the effects of preventive or therapeutic interventions? Despite the increased attention to PPP, most studies have done little more than codify the striking frequency with which this problem occurs after many disparate types of surgery: from inguinal herniorrhaphy to thoracotomy to breast surgery.[1] It is likely that the pathogenic mechanisms leading to PPP are multiple, and thus, more rigorous study design will be required to better understand how the problem evolves and who is at greatest risk. Such careful study design has been the exception rather than the rule. What we do know is that those that seem to be most relevant are gender, psychosocial factors, preoperative pain at the site of surgery or in other body regions, the type of surgical trauma, nerve damage, acute postoperative pain and inflammatory responses, perioperative analgesia, type of disease, recurrence of malignancy, and adjuvant therapy.[1]

Several years ago, the International Association for the Study of Pain defined PPP as a persistent pain state that is apparent more than 2 months postoperatively that cannot be explained by other causes (recurrence of disease, inflammation, and others). Most of the available literature has followed the lead of this overly simplistic definition and is composed of reports with insufficient pain assessment and little information regarding its consequences. Too often, studies on PPP have been conducted using a single assessment, asking patients simply to report whether they have persistent pain at one point in time using only a simple yes or no answer. Future studies should include not only a detailed assessment of the location, characteristics, and evolution of painful symptoms and associated changes in neurologic function but also assessments of the consequences of persistent pain on physical and social function. These studies must be performed on a procedure-specific basis because the type of surgery has different consequences on specific organ functions, and new assessment scales must be developed and validated for individual procedures. We have only limited information from validated procedure-specific scoring systems, the most comprehensive example being the post groin hernia surgery pain scale.[3] Finally, previous classifications of PPP as neuropathic and nociceptive pain have lacked specific objective criteria for such subgroupings, leading to the artificial concept that these two types of pain can be easily teased apart—even more damaging is the concept that the treatment for these two interwoven pain syndromes somehow differs. Indeed, many patients with PPP report both sensory abnormalities and localized stimulus-evoked pain, suggesting that both abnormal nerve function and ongoing nociception play a role in PPP.[4] Less than a handful of studies have included detailed neurophysiologic assessment of PPP.[4] There is a dramatic need for similar procedure-specific studies that are conducted prospectively to detail the evolution and characteristics of PPP and include pain-related functional impairment scales to assess the real impact of this problem.

The pathogenic factors involved in PPP may be divided into patient- and surgery-related factors, of which preoperative factors to be assessed in detail include psychosocial factors, pain and its consequences, nociceptive function,[1,5] and gender. Of the intraoperative factors, type of anesthesia, surgical approach (magnitude of tissue damage), nerve identification, and nerve injury are obviously important, and postoperative factors should include a detailed description of the type of analgesia, duration, early follow-up with neurophysiologic assessments, disease data, and detailed assessment of pain and its functional consequences. Although 2 months postoperatively has been proposed as a criterion for PPP, the definition was not based on procedure-specific data, and after some operations, a continuous inflammatory response may be apparent calling for assessments for at least 3–6 months postoperatively to provide useful information. Although these requirements for study design may seem obvious and easy to include in clinical trials, an example from a

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recent review on postthoracotomy pain details the major inconsistencies in the collection of pre-, intra-, and postoperative data that may influence persistent pain and thereby hinder precise conclusions about preventive and treatment strategies.[6] The same design problems are apparent in studies of other types of PPP.

A large proportion of the data in the PPP literature comes from retrospective patient questionnaires of differing quality and detail. Although such studies may provide useful hypothesis-generating data, they have inherent problems with recall bias of perioperative events and lack of possibility of assessing preinjury pathogenic factors. Such retrospective studies often report a relationship between patient recollection about the severity of their postoperative pain and the presence of chronic pain some months later and are undoubtedly flawed by such recall bias. Nevertheless, they have been useful to help in understanding the many factors to be included, but now prospective studies are required that incorporate a wide range of potential pre-, intra-, and postoperative factors, including storage of blood samples for future genetic analyses. Several gene candidates that seem to correlate with pain severity and the incidence of chronic pain are now available and are in need of study after different procedures.[7] Such characterization may help to understand the large interindividual variability in pain responses to nociceptive stimulation and the preoperative and early postoperative relation to development of PPP.[1,5]

One area that has received much attention from anesthesiologists is the role of anesthesia and perioperative analgesia in reducing the risk for developing PPP. These studies on "preemptive" or "preventive" analgesia have too often suffered from insufficient design and lacking the inclusion of established risk factors, thereby hindering interpretation. Most of these studies have not included detailed patient characteristics, including preoperative function of the nociceptive system, for example, the pain response to a standardized preoperative nociceptive stimulus.[5] Invariably, the duration of treatment has been too short, rarely extending beyond the duration of the surgery-induced inflammatory response.

There is general agreement that PPP is a significant clinical problem, and most will agree that we have too little information to recommend preventive or therapeutic interventions, and one of the primary reasons is the inadequacy of trial design and lack of prospective studies. To move forward—and with potential major implications for the understanding of other chronic pain states—studies on PPP should have an improved design including assessment of all of the known risk factors (table 1) conducted on a procedure-specific basis. In the beginning, new studies should include 3- and 6-month postoperative follow-up with sufficient follow-up on long-term outcomes to clarify whether persistent pain decreases over time (burn out). Until now, no such detailed long-term study has been reported in the literature. Many researchers are interested in this clinically relevant area—it is our hope that we can begin the much needed work of prospectively assessing how and why patients develop PPP using similar protocols across a wide range of different surgical procedures. Only with a better understanding of the natural history and consequences of this problem can we begin to design rational approaches to prevention and treatment.

Table 1. Elements of the "Ideal" Study Design of Persistent Postsurgical Pain

Preoperatively
Presence of preexisting pain (locally and remote)
Measurement of the functional consequences of preexisting pain
Neurophysiologic assessment
Psychosocial assessment
Analysis of "pain genes"
Intraoperatively
Descriptive characteristics about the incision
Descriptive characteristics about handling of nerves and muscles
Information about the disease being treated
Early postoperatively
Pain intensity and character
Pain treatment modality used
Neurophysiologic assessment
Late postoperatively
Pain intensity and character
Psychosocial consequences
Neurophysiologic assessment

Henrik Kehlet, M.D., Ph.D.,* James P. Rathmell, M.D.†
*Section of Surgical Pathophysiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark. †Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. jrathmell@partners.org

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