Preventing Chronic Postsurgical Pain

How Much of a Difference Makes a Difference?

AFTER surgical procedures such as amputation, mastectomy, and thoracotomy, as many as 60% of patients continue to experience pain for at least 6 months, with approximately 10% reporting severe pain.1–3 These chronic postsurgical pain conditions have major adverse effects on health-related quality of life, including physical functioning and emotional well-being. Unfortunately, the efficacy of existing treatments is limited and many patients remain refractory to currently available therapies. For this reason, the development of interventions that prevent chronic pain after surgery has the potential to have a major impact on public health.

Substantial attention has been devoted to the hypothesis that the incidence of chronic postsurgical pain can be reduced by “preventive” analgesia, and the benefits of preoperative, intraoperative, and postoperative analgesic interventions have been investigated alone and in various combinations. Although the results of these studies suggest that reduced acute pain and analgesic consumption can extend beyond the duration of action of the preventive analgesic interventions, there is little evidence that chronic postsurgical pain can be prevented.1,3,4 Placebo-controlled randomized clinical trials are needed to determine what specific analgesic interventions are efficacious for preventing chronic pain after what types of surgery for which patients.4–6

A critical component of future clinical trials will involve determining the clinical importance of the benefits of preventive analgesia. The results of recent studies and consensus recommendations provide a foundation for interpreting the benefits of chronic pain treatment;7,8 however, little attention has been paid to determining what magnitudes of chronic pain prevention are clinically meaningful. As is true of treatment benefits, evaluating the importance of preventive benefits involves a frequently misunderstood distinction between the interpretation of the clinical importance of individual patient benefits and the interpretation of the clinical importance of group differences.8

The results of multiple studies have shown that individual patients consider chronic pain reductions of at least 30% on numerical or visual analog scales to be moderately clinically important, whereas reductions of at least 50% represent substantial improvements.7,9 These thresholds are based on ratings by patients of their own improvement at the end of chronic pain trials, and consistent results have been found across different chronic pain conditions and in patients administered active treatments as well as placebo. Criteria for identifying clinically meaningful individual improvements are necessary to categorize patients as “responders” or “non-responders,” which makes it possible to compare the percentages of patients who achieve clinically important outcomes between different treatment and comparison groups.

Unfortunately, criteria for determining clinically important improvements in patients being treated for chronic pain cannot be extrapolated to those undergoing perioperative analgesic interventions to prevent chronic pain. Currently, there are no data that make it possible to determine whether patients who have not experienced chronic pain would consider its prevention after surgery important enough to undergo preoperative, intraoperative, and postoperative analgesic interventions. Evaluations of individual patient improvements associated with chronic pain treatments have emphasized pain reduction,7,9 but patients considering the prevention of conditions for which their risk is relatively low can also be expected to be particularly concerned with the adverse effects, safety risks, inconvenience, and costs of the preventive intervention.

It is likely that an efficacious preventive analgesia would not completely prevent chronic pain but would instead partially reduce its incidence, intensity, or duration. Such partial preventive benefits would, of course, be even harder for patients to evaluate; for example, would patients consider reducing pain intensity 6 months after surgery from a daily average of 4 to 2 on a 0–10 scale a clinically important benefit? Would this evaluation change if this reduction in pain intensity at 6 months is known to last for another 2 yr, or if the preventive intervention requires that patients take a medication that causes sedation, nausea, and constipation for 7 days before and 30 days after their operation? Evaluations of the clinical importance of preventive analgesia must reflect the magnitude of the reductions in chronic pain incidence, intensity, or duration that the intervention would provide. However, even small reductions in the incidence or intensity of a chronic pain condition that can last for months or even years might be considered clinically important by patients if...
they are considering a preventive intervention that is safe, well tolerated, and convenient.

Current approaches to the assessment of pain and other patient-reported outcomes require that the first step in developing new measures is to determine what patients themselves consider important, an approach endorsed by the United States Food and Drug Administration§ and others. To our knowledge, no studies have been conducted in which surgical patients or individuals in the community have been asked to evaluate the importance to them of preventing different intensities and durations of chronic postsurgical pain. There are several approaches that could be used to obtain such evaluations, including the discrete choice experiment. Until such research is conducted, it will be difficult to determine whether the specific benefits that might be provided by preventive analgesia are considered clinically meaningful by patients.

Although such research will provide an important foundation for future studies, it is crucial to recognize that the specific benefits that patients consider clinically important cannot be extrapolated to the evaluation of group differences. For example, a decrease from 4 to 2 on a 0–10 pain intensity scale might be considered a clinically important preventive benefit by individual patients, but it should not be concluded that a group difference of this magnitude in mean pain reduction between a preventive analgesic intervention and placebo is necessary for the benefit to be considered clinically important. It has been found that the treatment benefits that patients consider clinically meaningful are generally larger than the differences found between efficacious treatments and placebo in chronic pain trials.§ Improvements in individual patients reflect all effects, some not correctly attributed to the treatment, including regression to the mean and spontaneous resolution. However, differences between treatment and placebo groups reflect the incremental benefits of active treatments that contribute to improvement after subtracting placebo and other nonspecific effects.

Similarly, evaluations of the clinical importance of group differences in preventive benefits should not be based solely on what patients would consider a clinically important benefit for themselves. There are multiple factors that should be considered when interpreting the magnitude of the group difference (table 1), which must be conducted on a case-by-case basis. For example, whether a statistically significant difference in the prevalence of pain 12 months after surgery of 11% in patients who received preventive analgesia versus 28% in a comparison group12 is considered a clinically important difference will depend on various characteristics of the intervention, especially its overall risk–benefit ratio. Whether the benefits are considered clinically important can also depend on the specific outcome variable used; for example, is a difference in the percentage requiring analgesics at 12 months of 5% in the preventive analgesia group versus 14% in the comparison group more clinically important than the group difference of 11% versus 28% in the presence of any pain, no matter how mild?12

Efficacious preventive strategies would affect not only the individual but also the community at large. In light of the global increase in healthcare costs, the social costs and the economics of preventive therapies for chronic postsurgical pain need to be carefully considered. It has been argued that the recent focus on preventive health measures by politicians in the United States evades the critical question of whether such measures are more promising and cost effective than the treatment of existing conditions. A systematic review showed similar distributions of cost-effectiveness ratios for preventive measures and treatments, suggesting that the potential benefits of investing in prevention versus treatment are roughly equal. A recent study conducted in The Netherlands evaluated the cost effectiveness of a multidimensional low-back pain prevention program—which consisted of tailored education and work training, immediate physical therapy, and workplace ergonomic adjustments—and found that it failed to provide any additional beneficial effect or cost savings compared with a usual care control group. Strategies for preventing chronic postsurgical pain are more likely to be valuable from a cost–benefit perspective if a high-risk population can be identified, and the additional costs of the preventive measures are not excessive. Carefully conducted studies of the economics of preventing chronic postsurgical pain are essential to determine its social costs and benefits.

In all evaluations of preventive analgesia, the safety and tolerability of the specific interventions must play an especially critical role. The percentage of patients developing chronic postsurgical pain varies greatly depending on the specific surgery, patient risk factors, and the definition of chronic pain.13–14 Importantly, the risk of chronic pain can be quite low for many types of surgery, for patients without risk

Table 1. Factors to Consider in Determining the Clinical Importance of the Results of Clinical Trials of Preventive Analgesia

| Statistical significance of the primary efficacy analysis (typically necessary but not sufficient to determine that a preventive benefit is clinically important) |
| Magnitude of the absolute reduction in the incidence, intensity, or duration of chronic pain in patients receiving the preventive intervention |
| Safety of the preventive intervention |
| Tolerability of the preventive intervention |
| Results for secondary efficacy endpoints (e.g., preventing or attenuating adverse effects of chronic pain on health-related quality of life) |
| Convenience of the preventive intervention, especially its pre- and postoperative duration |
| Likelihood of patient adherence |
| Cost |

factors, and when chronic pain is defined as pain that is at least moderate in severity. Because of this, "if a preventive measure exposes many people to a small risk, then the harm it does may readily . . . outweigh the benefits, since these are received by relatively few."15

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