Commentary

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Lidocaine infusions and preventative analgesia: can the answer to our prayers be hiding right under our noses?

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For many pain medicine specialists, the prevention of chronic pain represents the pinnacle of our profession. The prevalence of persistent postsurgical pain (PPSP) varies from less than 10% to more than 50% depending on a multitude of factors, with 1 recent meta-analysis in young people finding a median prevalence of 20%.[9] Given the costs of treating chronic pain, coupled with the prevalence rate and rising number of surgeries, the annual economic cost of treating this epidemic is conservatively estimated to be in the billions of dollars in the United States. In previous articles by one of these authors and others, this quest has been described as the search for the Holy Grail, the pot of gold at the end of the rainbow, the light at the end of a dark tunnel, the will-o'-the-wisp, and an unachievable pipe dream.[5] An anesthesiologist was the founder of the International Association for the Study of Pain, and anesthesiologists represent a plurality of the membership. However, the creation of a subspecialty in pain medicine has led to a disconnect between interventional pain physicians and anesthetists, as well as the four other specialties now eligible for ACGME accreditation. The search for methods to prevent PPSP remains a shared interest between anesthesiologists and pain specialists, with ramifications that affect our surgical colleagues and primary care providers, who are often on the frontline of treatment.

In this issue of PAIN, Bailey et al.[2] present results from a systematic review and meta-analysis to test the hypothesis that the use of lidocaine infusions at the time of surgery reduces chronic pain at 3 months or longer after surgery. As an amide local anesthetic, lidocaine is approved by the U.S. Food and Drug administration both as an infusion for the acute treatment of ventricular arrhythmias and for production of local or regional anesthesia by infiltration techniques such as percutaneous injection and intravenous regional anesthesia, with the latter being a mainstay of anesthesiology. As enhanced recovery after surgery pathways have grown, lidocaine infusions have served as 1 tool to reduce opioid use. Outside of the immediate surgical period, clinical trials have examined the drug's ability to spare patients' chronic pain long after the short-acting drug has been metabolized by the body.

Based on data from 6 studies, the authors report that lidocaine infusions reduce the odds of chronic postsurgical pain by 71% and suggest based on these data that for every 5 patients treated with an infusion, one will be spared chronic pain. However, several limitations qualify these findings, many of which the authors acknowledge. Detecting changes in rare outcomes requires very large sample sizes, and studies on chronic pain after surgery remain statistically underpowered. Most of the trials evaluated recruited patients undergoing breast surgery, after which 30% to 50% of patients report PPSP. Conservatively assuming a 40% prevalence of PPSP after these high-incident surgeries, data on almost 1400 patients would be needed to detect an effect size of 6% (assuming alpha 0.05 and power 90%). Increasing the anticipated prevalence to 12%, as suggested in the authors' introduction, would still require more than 500 patients using the same assumptions. Clearly, the reported prevalence of chronic pain after surgery is intimately tied to how "chronic pain" is defined, and cursory yes/no responses used by many studies fail to appropriately capture chronic pain's impact as defined by standardized measures suggested in consensus guidelines.[6]

One of the key strengths of the study lies in its methodology, which, although not a Cochrane review itself, used a registered protocol that built on evidence from a previous Cochrane review and used standardized methods in line with the Cochrane Handbook, including searches of the gray literature.[4] In addition, the analysis of the primary outcome demonstrated no statistical heterogeneity, which suggests that little variation existed in the effects evaluated in all 6 studies. Importantly, reporting bias seems less likely given that studies evaluating generic lidocaine, which was first synthesized and marketed in the 1940s, are not generally industry funded, as many studies evaluating other pharmacologic products as preventative analgesics are (eg, membrane stabilizers and antidepressants). Research has shown that industry-sponsored studies are 3.6 to 4 times more likely to yield positive findings, which can significantly alter alter the interpretation of results and the cost:benefit analysis.[3] On the other hand, findings from systematic reviews and meta-analyses are only as valid as the trials from which conclusions are based. In this case, all trials except one contained at least 1 high risk of bias domain, only 2 reported outcomes at 6 months, and only 1 adjusted results based on possible risk factors for chronic pain. Flaws in study design and statistical analysis may distort findings in ways difficult to correct, leading to the all-too-commonplace expression in pain medicine,

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"garbage in, garbage out." Although a sensitivity analysis excluding low-quality studies is often the next step to control for methodological shortcomings, in this instance, only 1 study would remain.

Potential pharmacological mechanisms exist for lidocaine to prevent postsurgical pain, given its ability to reduce dorsal horn activity and possible antagonistic effects at the *N*-methyl-D-aspartate receptor, leading to a potential reduction in peripheral and central sensitization. Lidocaine may also spare opioid consumption, which can lead to hyperalgesia and also contribute to PPSP. Other beneficial characteristics of lidocaine include its relative safety, low cost, and ease of administration through the intravenous route. Compared with alternative methods commonly used to prevent PPSP such as nerve blocks, which themselves may be associated with persistent pain, and parenteral treatments such as gabapentinoids, which can result in postoperative sedation and delayed discharge,[10] the risk: benefit scale is tipped in favor of lidocaine.

One could reasonably argue that most chronic pain conditions begin with an "inciting event," although the mechanistic basis for causation is sometimes unclear. For example, some studies have found that most people with low back pain, the leading cause of disability in the world, report a traumatic onset irrespective of anatomical pathology.[7,8] Even for fibromyalgia, which is widely acknowledged to be a disorder of central pain processing, around 40% of individuals claim an inciting event.[1] What distinguishes surgery from noniatrogenic forms of trauma is that we can prepare for this collision before it happens. The "billion dollar" question then becomes whether this prescience leads to the development of interventions that ultimately change the natural course of surgical history.

Conflict of interest statement

The authors have no conflict of interest to declare.

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This editorial discusses an off-label use of an FDA-approved medication.

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