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Intravenous Lidocaine to Treat Postoperative Pain Management

Novel Strategy with a Long-established Drug

MANY surgical patients still experience moderate to severe pain after surgery, despite efforts to develop new drugs and techniques for postoperative analgesia. We have recognized for some time that postoperative pain is not only a transient, uncomfortable experience for the patient, but can also have long-term sequelae, including chronic pain.[1] In addition, adequate control of postoperative pain represents one of the most important factors in determining the time when patients can be safely discharged from a surgical facility. Adequate postoperative analgesia clearly enhances patient satisfaction and facilitates earlier mobilization and rehabilitation. Although perioperative analgesia has been traditionally provided by systemically administered opioids, extensive use of opioids is associated with a variety of perioperative side effects that can delay hospital discharge. Therefore, surgical patients would greatly benefit from a perioperative analgesic regimen that is effective, has minimal side effects, demonstrates a wide margin of safety, and can be easily managed away from the hospital. Practitioners are increasingly turning to alternatives to systemic opioids, including epidural or perineural infusions, for managing pain during the perioperative period to minimize the adverse effects of analgesic medications. These methods are cumbersome and expensive to apply, and recent studies using a simpler approach, intravenous lidocaine infusion, have shown significant beneficial effects.[2–4] In the current issue of ANESTHESIOLOGY, Kaba *et al.*[2] demonstrate, using a randomized, controlled, double-blind design, that a simple infusion of intravenous lidocaine produced effective analgesia after laparoscopic colectomy and allowed for a more rapid rehabilitation and quicker hospital discharge.

Systemic administration of lidocaine has previously been demonstrated to have analgesic actions in patients with chronic neuropathic pain.[5] The prolonged effect of lidocaine is thought to reflect its inhibition of spontaneous impulse generation arising from injured nerve fibers and from dorsal root ganglion neurons proximal to the injured nerve segments[6] and by suppressing primary afferent-evoked polysynaptic reflexes in the spinal dorsal horn.[7] These effects are thought to be mediated by a variety of mechanisms, including sodium channel blockade,[7] as well as inhibition of G protein–coupled receptors[8,9] and *N*-methyl-D-aspartate receptors.[10] In addition, intravenous lidocaine is an effective modality for treating visceral pain.[11] Postoperative pain after abdominal surgery includes many forms of distress, such as spontaneous pain at rest; pain during movement, including that of respiration; and visceral pain arising from damage to internal organs during surgery. Based on these observations and the similarity in some underlying processes of postoperative and neuropathic pain, systemic administration of lidocaine might be expected to improve postoperative pain and discomfort and aid in better mobilization. In addition, lidocaine would predictably have a greater effect when administered perioperatively, *i.e.*, during the presence of significant nociceptive input. Kaba *et al.*[2] emphasized that perioperative (before, during, and after surgery) intravenous infusion of lidocaine, in a low dose as used for the treatment or prophylaxis of ventricular arrythmias,[8] was able to improve postoperative analgesia.

Rimback *et al.*[12] and Groudine *et al.*[4] have shown that continuous intravenous lidocaine infusion provided a faster return of bowel function after surgery. Similarly, in the study of Kaba *et al.*,[2] systemic lidocaine improved postoperative bowel function, as evidenced by shortened times to first flatus and defecation after surgery. Postoperative ileus results from several etiologies, including postoperative opioid consumption, visceral inflammation secondary to surgery, and postoperative sympathetic stimulation. Which of these are most affected by systemic lidocaine remains a subject for future study, but the patient benefit is clear and now reproduced in several studies.

So where does intravenous lidocaine sit among treatments of moderate to severe postoperative pain? Continuous epidural infusion and continuous peripheral nerve blocks have been applied with increasing frequency for the management of postoperative pain and clearly improve analgesia compared with traditional methods. In Japan, most anesthesiologists prefer continuous epidural analgesia over systemic opioids for the management of pain after abdominal surgery. Although most studies indicate that epidural and peripheral nerve block techniques provide superior analgesia (particularly when local anesthetics are used) compared with systemic opioids, whether they reduce morbidity and mortality remains a subject of controversy and research.

We are becoming increasingly aware of the risks asso-

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ciated with the use of invasive techniques in the treatment of postoperative pain, and how the clinician can properly weigh the risks and benefits of these techniques on an individual basis is uncertain. The study by Kaba *et al.*[2] suggests that intravenous lidocaine may be considered as another option in this setting to accelerate acute rehabilitation and facilitate earlier patient discharge. Epidural infusions are certainly more expensive and invasive than intravenous infusions. Furthermore, modern thromboprophylaxis practice with low-molecular-weight heparins often preclude the use of continuous epidural therapy because of the concern over risk of epidural bleeding and hematoma with catastrophic outcomes due to spinal cord or nerve root compression. The safety of intravenous lidocaine for postoperative analgesia is far from assured by small studies such as those currently available, and there is an accumulation of lidocaine in the blood during the period of infusion, even at these low doses.[2] Although many studies have reported that the therapeutic dose of lidocaine for ventricular arrhythmias remains well below toxic concentrations,[8] whether this applies in the postoperative setting with the multiple influences on drug distribution and elimination remains unknown. Therefore, intravenous lidocaine is appealing as a simple and inexpensive method to gain the same benefits as more invasive and costly techniques, but we currently lack large numbers of patient exposures to define its safety and direct head-to-head comparisons to compare its efficacy.

As in all areas of medicine, we search in postoperative pain management for an ideal drug or technique that is effective, simple, inexpensive, and safe. Further studies are needed to clarify and establish where intravenous lidocaine sits in the spectrum of currently available agents in this regard. The best dose of lidocaine to obtain maximum efficacy for postoperative treatment of somatic and visceral pain and improved bowel function while minimizing adverse effects has not been defined. But studies like that of Kaba *et al.*[2] with this relatively novel strategy using a long-established drug may help to develop and implement effective therapeutic management strategies to improve our treatment of postoperative pain and perioperative morbidity.

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Racial and Ethnic Disparities in the Quality of Pain Care

The Anesthesiologist's Call to Action

ENSURING healthcare quality (*i.e.*, access to health care, effectiveness, and efficacy) while optimizing health and quality of life has tremendous benefits to the individual and to society. However, the Institute of Medicine (IOM) series of books resulting from the Quality of Health Care in America Project provides startling evidence for medical errors, variability in healthcare quality, and a quality gap that puts patients at risk for increased morbidity and mortality.[1,2] As documented in the congressionally mandated IOM report *Unequal Treatment: Confronting Racial and Ethnic Disparities in Healthcare*, stark differences in health and the healthcare experience based on race, sex, age, socioeconomic status, and community

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characteristics exist.[3] In an increasingly diverse America, disparities in health and health care are critically important to our nation's colloquial health. The IOM identifies two sources of disparities: (1) healthcare systems and the legal and regulatory climate in which they operate and (2) discrimination such as biases, stereotyping, and uncertainties in clinical communication and decision making.[3] Using a statewide database, the article by Glance *et al.*,[4] "Racial Differences in the Use of Epidural Analgesia for Labor," provides additional evidence for differential access to epidural analgesia. Overall, Glance *et al.* show that black and Hispanic women were significantly less likely to receive epidural analgesia during labor than white women. Although differential access to labor epidurals based on race were described previously, Glance *et al.* extend the literature by revealing that these differences persist even when insurance coverage, provider, and clinical characteristics are similar, thereby providing evidence for physician variability in decision making.

Among the many overarching goals stated in *Healthy People 2010* is improving health and eliminating disparities in health care for all Americans.[5] Several federal agencies (*e.g.*, National Institutes of Health, Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality) identified health and healthcare disparities as one of the nation's top strategic priorities. They further supported several initiatives designed to reduce and eliminate disparities in health and health care. Clearly, creating new knowledge directed at understanding and addressing health and healthcare disparities is vitally important. Although the IOM study on healthcare disparities provides information on pain management, the committee's work focused primarily on an acute injury and cancer pain model. Pain has significant socioeconomic, quality of life, and health implications; however, pain as a public health issue, the quality of pain care, access-related factors, physician variability in pain management decision making, and access to analgesics were not addressed in a substantive manner in the IOM reports.

Overall, disparities in health and health care increase healthcare costs and diminish quality of life while increasing morbidity and mortality. The Joint Commission on Accreditation of Hospitals and Healthcare Organizations pain management standards, requiring accredited institutions to ensure that all patients have pain assessed, provided necessary attention to a multitude of factors influencing pain management. Anesthesiologists often lead the continuous quality improvement efforts directed at optimizing pain management in the perioperative period and throughout their institutions. For many advocating for pain management and improvements in the quality of pain care in particular (*e.g.*, patients, researchers, clinicians, pain medicine physicians), the Joint Commission on Accreditation of Hospitals and Healthcare Organizations standards seemed to be the tipping point for addressing pain complaints in a comprehensive and multidisciplinary fashion. However, the literature continues to document suboptimal pain assessment and the undertreatment of pain.[6] Furthermore, the literature supports variability in pain management decision making and disparities in pain care for all types of pain, *i.e.*, acute, chronic, and cancer pain, as well as pain associated with terminal illness, especially for racial and ethnic minority persons.

Overwhelmingly, the literature supports that the pain complaints of racial and ethnic minorities, women, and elderly persons are often unheard.[6] The cornerstone for quality pain care is pain assessment, but the bulk of the literature supports that minorities are less likely to have their pain assessed, yielding an unequal burden due to pain. When their pain is assessed, minorities often receive less pain medication than their white counterparts, suggesting physician variability in decision making. When receiving a prescription for opioid analgesics, minorities are less able than whites to fill opioid analgesic prescriptions in their local pharmacies, regardless of income.[7] Whereas income is protective for whites, income is not protective for higher-income minorities who experience problems similar to those of low-income minorities in obtaining prescription opioid analgesics in their local pharmacies but have less access than low-income whites. Many believe that most health and healthcare disparities are reduced or even eliminated when socioeconomic factors are controlled. Glance *et al.*[4] confirm the role insurance plays in accessing labor epidurals where women with private insurance have the best access to this modality for pain relief. However, consistent with the literature, Glance *et al.* also reveal that insurance status may not be protective for black women. Although there was no difference in epidural use among black women with private health insurance and black women with Medicaid or no health insurance, black women with private health insurance had the same rates of epidural use as white women without insurance.

Despite the critical importance of race and ethnicity in health and health care and amid the success stories of improvements in quality, continuing disparities in health and health care provide a sobering reminder that we are not there yet. In fact, our failure to attend to disparities based on race, ethnicity, sex, age, insurance, socioeconomic status, and community characteristics contributes to increased morbidity and mortality while increasing healthcare costs. Throughout the perioperative period, anesthesiologists continue to provide innovative leadership in the continuous quality improvement and pain management arenas. However, in an increasingly diverse and aging America, few anesthesiologists have embraced our nation's most important public health and quality of care problems: disparities in health and health care in

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general and disparities in pain care in particular. The intrinsic value of anesthesiologists addressing disparities in pain care in a substantive manner is tremendous considering their demonstrated expertise in addressing patient safety and reducing medical errors.

The representation of women as well as racial minorities in research and in the healthcare professions (including anesthesiologists) is far less than their representation in the general population. Even more problematic is research showing that most graduating residents believe that they have not received training on how to provide culturally competent care. Therefore, it is not surprising that miscommunications frequently occur with patients leading to the potential for difficulties in providing quality health care. Overall, we know little about how patient factors (*e.g.*, their preferences, language, cultural beliefs, family, support systems, decision making) influence pain care.

Clearly establishing an interdisciplinary pain disparities research agenda is imperative to inform our clinical care if healthcare disparities are to be reduced and eventually eliminated. However, several challenges exist. Only a small percentage of research dollars is directed at health services research, health disparities, and pain research. Racial and ethnic identifiers are infrequently used to monitor health outcomes. However, these indentifiers are critical to understanding variations in quality and variability in decision making if important insights are to be identified to improve the quality of health care for all Americans.

Our ability to reduce and eliminate disparities in pain care has significant public health and policy implications. Toward that end, multidisciplinary approaches are necessary to improve the quality of pain care, thereby reducing and eliminating disparities in care. Clinical and research efforts must be informed by the patient as a full healthcare partner if we are to clarify their preferences and to improve the quality of health care. By improving the quality of pain care for those most vulnerable to variations in quality and decision making, we can improve health and the quality of pain care for all. Real improvements in the quality of pain care will occur when we view the failure to assess and treat pain as a medical error!

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Anesthetic Neuroprotection

Some Things Do Last

DO anesthetics protect the brain from ischemic injury? The answer to a seemingly simple question has eluded researchers for more than a quarter of a century. The contribution by Sakai *et al.*[1] in this issue of ANESTHESIOLOGY suggests that we may finally have an answer to at least part of the long-standing controversy—at least in rats.

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Working with laboratory rats, Hiroaki Sakai and coworkers in David Warner's laboratory at Duke University show conclusively that isoflurane is neuroprotective during focal cerebral ischemia and that, in distinction to several other influential studies,[2,3] the protection from isoflurane is long-lasting, evident for a month after the experimental stroke.

To understand the significance of the article by Sakai *et al.*, some history of investigations regarding anesthetic neuroprotection is in order. Disputes regarding whether clinical anesthetics confer neuroprotection in experimental models of brain ischemia date to the late 1960s. John Michenfelder at the Mayo Clinic argued that because even very-high-dose barbiturates do not reduce brain metabolism more than does brain ischemia, barbi-

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turates should not be protective after cardiac arrest or global ischemia.[4] Correspondingly, clinical trials in human cardiac arrest were negative,[5] but barbiturates did seem to be beneficial in experimental focal ischemia.[6] As time passed, numerous studies pro and con appeared, examining a wide range of different models and anesthetic agents. The controversy continued through the 1980s, when it became clear that even small changes in brain temperature during or after ischemia had a major impact on outcome, with hypothermia being protective and mild hyperthermia being deleterious. A new wave of experimentation with volatile anesthetics ensued, based on the knowledge that hypothermia was a confounding variable in previous neuroprotection studies with these agents. Of note, similar issues vexed studies on human neuroprotection: barbiturate neuroprotection after coronary artery bypass graft surgery was reported by Nussmeier *et al.*,[7] only to be refuted by Zaidan *et al.*[8] when postbypass hypothermia was prevented. However, in experimental ischemia, agents like isoflurane remained viable neuroprotectants even when intraischemic and postischemic brain temperature was carefully controlled.[9] But doubts persisted, and neuroprotection advocates[10] continued to clash with critics.[11] Soon the pendulum swung decidedly in the negative direction, when the durability, rather than the potency, of anesthetic protection came into question. Seminal studies by Kawaguchi and others found that although isoflurane decreased the degree of injury present several days or a week after the ischemia, animals given isoflurane fared just as poorly as controls when examined several weeks to a month afterward.[2,12] That is, isoflurane protection fades. That anesthetic neuroprotection is transient was further supported by work of Elsersy *et al.*[13] and Bayona *et al.*[14] These investigations revealed that in rodent forebrain ischemia and focal ischemia models, respectively, anesthetic protection was not sustained.

Clearly, the results of these previous investigations differ from those of Sakai *et al.*, and an explanation of this discrepancy requires a close examination of the experimental model that was used. Sakai's control group for the stroke treatment notably involved awake rats—an experimentally difficult preparation involving intensive care and observation of study animals. All previous studies performed with modern standards of blood pressure control, adequate respiratory monitoring, and preservation of normothermia used nitrous oxide-fentanyl–anesthetized rats in the control group, possibly obscuring the benefits of the inhalation anesthetic.

Another important feature of the Sakai study is that the experimental ischemia model involved a 50- or 80-min temporary, rather than permanent, occlusion of the middle cerebral artery. This injury, although severe, was not as severe as the permanent occlusion group used by other investigators including Kawaguchi and others. As suggested by David Warner, perhaps these other studies were asking too much of any potentially neuroprotective agent to protect against permanent middle cerebral artery occlusion.[15] In fact, the work of Christian Werner's group indicates that volatile agent neuroprotection can be sustained provided the injury is of mild to moderate severity.[16] It seems clear that given the right circumstances, anesthetics can achieve enduring neuroprotection.

The current studies raise several questions. One of the more interesting is whether neuroprotection is intrinsic to the state of anesthesia or is dependent on some particular quality of isoflurane distinct from its capacity to produce unconsciousness and prevent movement from a noxious stimulus. As noted, the use of an awake control group experiencing ischemia was probably critical to the outcome. Further studies with different anesthetic agents and with mechanism-based examinations of neuroprotective actions should be able to reveal the answer to this question.

An important question is whether the findings of Sakai *et al.* will renew interest in testing anesthetics in human neuroprotection trials, an effort that had clearly waned after the failure of countless clinical studies of stroke neuroprotection. An examination of preclinical data demonstrating the neuroprotective efficacy of mild hypothermia may provide some perspective. In a variety of models of ischemia, and in a variety of species, mild hypothermia was shown to be profoundly neuroprotective. Moreover, this protection was demonstrated months after the ischemic injury.[17] Based on these indisputable results, clinical trials of mild hypothermia in head-injured patients were initiated; the failure of hypothermia to improve outcome[18] in these patients was met with disappointment. Similarly, in patients undergoing intracranial aneurysm clipping, hypothermia did not provide any benefit.[19] If an intervention that has, arguably, shown effective neuroprotection in preclinical studies fails in clinical trials, what then are the prospects for demonstrating the neuroprotective efficacy of anesthetic agents given the disparate findings of anesthetic protection in preclinical investigations? Clearly, much more work is needed before isoflurane can be evaluated as a neuroprotectant, especially considering the large and expensive clinical trial that necessarily lies ahead. In today's environment of outcomes research driving evidence-based clinical practice, whether it is even possible to obtain good evidence for anesthetic neuroprotection in humans is a matter for debate. But the study by Sakai *et al.* provides strong rationale for such clinical research.

Is the story of anesthetic neuroprotection nearing its final chapter? Although the contribution of Sakai *et al.* is a major step in neuroprotection in the laboratory, history teaches us that much more remains to be written in the clinic.

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