**Postoperative Visual Loss**

**Experts, Data, and Practice**

PLEASE allow me to paraphrase recent plaintiffs’ experts in cases related to postoperative visual loss (POVL) in patients who had undergone spine surgery while positioned prone.

The anesthesiologist clearly caused this patient’s vision loss by letting the mean arterial blood pressure drop below 60 mmHg for more than 5 min. This patient is now blind because the anesthesiologist let the patient’s hematocrit level decrease to less than 24% during the case. The person providing the patient’s anesthesia failed to avoid prolonged pressure on the eye, leading to the patient’s ischemic optic neuropathy and blindness.

No one wants any patient to experience a catastrophic perioperative event such as permanent blindness. However, these statements (and others similar to them) are devastating to the anesthesiologists who have provided apparent good care to patients undergoing spine procedures, only to find that their patients have awakened with near complete loss of vision in one or both eyes.

What is wrong with these statements? First, these plaintiff “experts” are making statements for which there are no supporting data. Second, good anesthesiologists experience loss of confidence and, in some cases, shattered practices while these legal actions are being resolved. Last, these statements detract attention and effort from the development of studies to determine the etiologies of, and possible preventive measures for, perioperative blindness. Our patients deserve better.

Postoperative visual loss is a real problem in patients undergoing cardiac and spine surgical procedures. POVL occurs more frequently in cardiac surgical patients. There seem to be multiple etiologies for POVL in cardiac surgical patients (e.g., embolic, thrombotic, oncotic, and ischemic reasons), several of which may be related to the surgical procedures and operative techniques themselves. These patients have numerous visual pathologic consequences, including central retinal artery occlusion and ischemic optic neuropathy (ION). Because there are many factors that may contribute to the development of POVL in cardiac surgical patients, it is a difficult problem to study.

In contrast, POVL in patients undergoing spine surgery entices us with the potential to discern etiologic factors in a group of patients who have less variation in visual pathology and outcomes. Dr. Lee et al. report these findings this month in their review of the first 6 yr of cases submitted to the American Society of Anesthesiologists Postoperative Visual Loss Registry. This registry was established in 1999 after anesthesiologists and others voiced concern that the frequency of POVL seemed to be increasing, particularly in patients undergoing spine surgery. In their comprehensive report of 93 cases of POVL in patients undergoing spine surgery, the authors note that 89% of the patients developed ION, with the other 11% of patients experiencing central retinal artery occlusion. Most patients with central retinal artery occlusion had evidence of ocular trauma and unilateral visual loss, suggesting that in some instances, positioning or other potentially controllable factors may have played a role. Many of the patients with ION had bilateral visual loss, suggesting that one or more systemic factors, including inherent patient-specific factors, may have been present. In the patients with ION, the highest-risk group included patients who had anesthetics lasting more than 6 h and estimated blood loss of greater than 1 l. The authors were unable to find any factor under the direct control of anesthesiologists that led to a high frequency of ION. Specifically, patients who developed ION had intraoperative mean arterial blood pressures and hematocrits that ranged widely, with patients at each extreme of these parameters developing ION.

What is the typical natural history of ION in spine surgery patients? After awakening, the patients often note an inability to see, citing that they can only perceive gray shadows (usually in response to objects in motion). An ophthalmologic examination may show an edematous optic disc if the ischemia is associated with the anterior portion of the optic nerve, but more often there are no acute funduscopic findings. The papillary light
reflex may be reduced or absent, but this finding, too, often is difficult to discern. Imaging of the visual pathways by magnetic resonance or computed tomography is usually fruitless but may be worthwhile to confirm the absence of other pathologic changes (e.g., cerebral infarction or hemorrhage). As demonstrated by Dr. Lee et al., vision rarely is improved over time from the initial impaired postoperative status.

A recently published American Society of Anesthesiologists Practice Advisory provided several important findings:

The use of deliberate hypotensive techniques during spine surgery has not been shown to be associated with the development of perioperative visual loss. At this time, there is no apparent transfusion threshold that would eliminate the risk of perioperative visual loss related to anemia.

These findings seem to be confirmed by data from the current article and negate the veracity of the first two statements above that are paraphrased from plaintiffs’ experts. The current article also reports that none of the 83 spine surgery patients who developed ION had periorbital or ocular findings suggestive of intraoperative trauma or externally applied pressure, thus negating the third statement paraphrased above.

Unfortunately, the current article does not advance our understanding of potential etiologic factors that cause ION in spine surgery patients except for the confirmation that the highest-risk patients are those who undergo anesthetics greater than 6 h in duration and who experience intraoperative blood loss of more than 1 l. How can we best use this information? First, we should consider informing patients in this high-risk group that there is a small, unpredictable risk of POVL. Second, we should collaborate with our surgical colleagues to consider staging spine procedures in these high-risk patients in an effort to reduce prolonged, bloody procedures in patients who are positioned prone. This latter suggestion has been endorsed by the North American Neuro-Ophthalmology Society and supported by the North American Spine Society.

In summary, Dr. Lee et al., along with the American Society of Anesthesiologists, should be congratulated for providing data that at least help us to identify patients undergoing spine surgery who fall into a high-risk group for POVL. Ironically, their data also tell us what we do not yet know about POVL. The current article provides important information that, if examined responsibly by plaintiffs’ “experts,” should reduce the frequency of unsubstantiated claims and promote a more informed and fair resolution of legal actions.

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References

Retrospective Analysis

Looking Backward to Point the Way Forward

The first rule of discovery is to have brains and good luck; the second is to sit tight and wait until you get a bright idea.¹

ANESTHESIOLOGISTS know well that high-quality research involves both generating and testing hypotheses. Generating high-quality hypotheses is becoming more important as funding decreases and scrutiny increases, and methods for developing hypotheses have been published.² One fruitful approach to hypothesis generation focuses on the use of previously collected data to reveal undiscovered causalities. Consequently, retrospective research, such as the article by Exadaktylos et al.³ in this issue of ANESTHESIOLOGY can be viewed as the hunt for questions rather than answers.

Exadaktylos et al.³ performed a retrospective cohort study comparing the effect of paravertebral blockade in addition to general anesthesia in altering recurrence and metastasis of breast cancer after mastectomy. Recurrence- and metastasis-free survival was 94% (95% confidence interval, 87–100%) and 82% (74–91%) at 24 months and 94% (87–100%) and 77% (68–87%) at 36 months in the groups that did and did not receive paravertebral blockade, respectively (P = 0.012). It is tempting to dismiss these findings outright for many reasons, including inherent bias of retrospective studies, biologic implausibility, and their small cohort size; all of these issues will be addressed below. However, we strongly agree with the authors’ intent of proposing their findings as a possible benefit in need of prospective verification. Such a two-phased approach should be the model for discovery of moderate treatment effects that would require large-scale trials to prove, because large prospective trials should only be undertaken when there is significant support for the hypothesis.

Bias in retrospective studies is a serious threat to the validity of the findings. Bias can come in a myriad of forms, and it may be impossible for statistical analysis to detect and eliminate bias.⁴ Recently, propensity scores are increasingly being used to help determine whether the outcome differences seen are true effects of the treatment or just a sign that the risk factors for the outcome were not evenly distributed between the groups. Propensity scores are different from regression analyses because they take into account the variable’s influence on the likelihood for the subject to receive treatment, the variable’s impact on outcome, and the variable’s impact on the relationship between treatment (or nontreatment) and outcome.⁵ Such analyses increase in importance in studies where randomization is impossible or impractical. However, it remains controversial whether anything other than randomization of more than 50 patients (per center) can ever equally distribute unknowns so that they do not confound the relationship between treatment and outcome.

Assuming that chance, bias, and confounding are unlikely explanations of the association of paravertebral blockade to improved recurrence-free survival, we must judge the likelihood of a cause–effect relation in the manner proposed by Sir Austin Bradford Hill, a preeminent British biostatistician, by examining several factors, including biologic plausibility.⁶ Biologic plausibility demands that a possible association fits existing biologic or medical knowledge. This is a potentially double-edged guide, because one is only likely to look for what one expects or is prompted to see, but at the same time, it helps to reign in the overuse of exploratory analyses from areas of erroneous association.

Exadaktylos et al.³ have proposed a bold link between paravertebral blockade and reduced cancer recurrence. The preservation of immunologic function in the paravertebral blockade group is cited as the cause for decreased recurrence and metastasis. Although there is some basic science research that frames their exciting theory, thoracic paravertebral block with 0.5% bupivacaine (1.5 mg/kg) has been shown to block somatosensory evoked potential transmission reliably only at the dermatome of injection.⁷ Further, 0.25% bupivacaine has been shown to produce far less inhibition of somatosensory evoked potentials than 0.5% bupivacaine.⁸ Consequently, the 0.2 ml/kg of 0.25% levobupivacaine bolus (plus infusion) used by Exadaktylos et al.³ seems insufficient to inhibit the stress response enough to allow unfettered immunologic function.

Randomization of subjects in large prospective studies seems to avoid the possible biases of retrospective and unrandomized studies. The difficulty is deciding what questions should be answered because as we search for smaller effects, we require dramatically larger groups of subjects to study. Therefore, we have the ethical issues

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of limiting resources to specific questions and avoiding the unethical use of subjects in studies that would be too small to produce a reliable answer. The article by Exadaktylos et al.\(^3\) can be seen as an example to use current and past clinical care databases to produce preliminary data, which helps to focus future research by highlighting a possible benefit and also by estimating an effect size that allows for a more precise and thus economical enrollment target. Consequently, we are in favor of publishing high-quality retrospective studies, but we demand strict guidelines on quality (discussed below), and we strongly caution against bias not to publish high-quality retrospective studies where no relation between predictors and outcome has been demonstrated. Such publication bias could lead to subjects’ being enrolled in studies where there should have been published reasons to believe that no effect would be seen.

Guidelines have been proposed for data collection from medical records for use in retrospective analyses to avoid biases from using data collected for patient care.\(^9\) These guidelines indicate two major risk categories: poor information flow from the patient to the medical record and poor information flow from the medical record to the research database. Poor information flow from the patient requires verification from original source documents and multiple physicians’ notes. When a key element, exposure, or risk factor is sought, a random sample of patients should be surveyed, with the survey being the accepted standard against which the abstracted data are judged.

Poor information flow from the medical record to the research database encompasses both the availability of the needed data in the medical record and the ability to extract the data in an unbiased fashion. Reviewing peer-reviewed studies with a focus on the method sections, discussions with expert clinicians, and input from biostatisticians and epidemiologists are critical to determining what data are needed both to answer the question and to minimize confounding. The next step is a pilot study to determine whether the necessary data are available from the medical records. Bias is further reduced by using blinded data collectors who have an appropriate paramedical education and who are armed with case report forms with clearly adjudicated definitions of disease, exposure, and confounders. The work of the data collectors should be compared with control interobserver variability, and random checks of the case report forms against source documents will further help to control error.

The aging population will require increased perioperative care during a time of shrinking federal and private funding for research. The heightened scrutiny of the federal, private, and public sectors for improved outcomes will put anesthesiologists, as leaders in safety and quality improvement, in an ideal position to direct and lead trials to improve outcomes of our patients. Ethics, reality, and economy direct us to take advantage of accumulated clinical cases to help develop and guide future trials. It is therefore incumbent on anesthesiologists to use the tools, guidelines, and expertise of epidemiologists and statisticians to produce the most informative trials possible. It is also incumbent on journal reviewers and editors to balance enforcing best scientific literature practice with the need for thought-provoking articles that stimulate new areas of research and heated discussion; this intellectual tension can only improve academic anesthesiology.

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Unraveling the Mysteries of Sleep-disordered Breathing in Children

IN this issue of Anesthesiology, two complementary and fascinating studies focus our attention on chronic intermittent nocturnal desaturation (CIND) in children with sleep-disordered breathing (SDB). In the first study, Moss et al.1 exposed developing rats to chronic intermittent hypoxia during their sleep cycle and found that they were more sensitive to the respiratory depressant effects of opioids than nonhypoxic rats. In the second, Brown et al.2 determined that children whose minimum nocturnal desaturation was less than 85% required one half the dose of opioids for similar pain scores after tonsillectomy and adenoidectomy (T&A) surgery compared with children whose minimum saturation was 85% or greater. These observations provide compelling evidence for the cautious and individualized dosing of opioids in children with SDB.

Sleep-disordered breathing is a continuum that ranges from normal breathing to obstructive sleep apnea (OSA).3–5 SDB is caused by a narrowing of the upper airway, which in turn may be attributed to adenotonsillar hypertrophy, decreased neuromuscular tone, obesity, and/or craniofacial abnormalities. As the severity of the airway resistance increases, hypercapnia, hypoxia, and/or intermittent upper airway obstruction begins to develop. Polysomnography is the accepted standard for diagnosing SDB and its level of severity, although its use in children has been limited. For most children who present for T&A surgery, the diagnoses of OSA and other SDB patterns are largely based on clinical criteria and/or portable techniques (i.e., nocturnal oximetry), although neither can reliably predict OSA.6,7

With an increasing number of children with a diagnosis of OSA presenting for T&A surgery, understanding the nature of the 10-fold greater incidence of perioperative respiratory complications in those with OSA compared with those without has become paramount.8–10 In a retrospective review, Wilson et al.10 noted that four factors increased the risk of perioperative respiratory complications after T&A surgery, including CIND. They noted that the incidence of respiratory complications was two and one half times more common in children whose minimum nocturnal saturation was less than 80% compared with those whose saturation was greater than 80%.10 Their observations were consistent with a prospective study by Waters et al.,11 who reported that children with OSA undergoing T&A surgery demonstrated diminished minute ventilation during spontaneous ventilation with halothane but, more importantly, demonstrated a 10-fold greater incidence of apnea after fentanyl (0.5 μg/kg) compared with children without OSA. The attenuated ventilation during halothane is consistent with the flattened carbon dioxide response reported in children with OSA.12 However, the greater incidence of apnea after fentanyl in children with OSA was surprising. Brown et al.13 subsequently confirmed these observations, noting that perioperative morphine requirements in children with OSA correlated with age and the severity of nocturnal desaturation.

Is CIND, in isolation, sufficient to alter opioid sensitivity? Moss et al.1 investigated the respiratory responses to opioids in developing rats that were rendered intermittently hypoxic during their diurnal sleep cycle. They found that hypoxic rats were more likely to develop apnea in response to fentanyl than normoxic rats.1 In humans, however, CIND is unlikely to occur in isolation. Rather, it occurs in combination with a pathologic condition such as OSA. These data from rats suggest that CIND, not OSA, is the putative trigger for the increased opioid sensitivity observed.

Knowing that the respiratory and analgesic effects of opioids are tightly linked to μ-subreceptors, Brown et al.2 posited that children with CIND may require less opioid for posttonsillectomy analgesia than those without CIND. Not surprisingly, they found that children whose minimum saturation was less than 85% required one half the dose of opioids as those whose minimum saturation was 85% or greater for the same pain scores.2 The theme echoed by all of these studies is that children with OSA/CIND are very sensitive to opioids.

The molecular basis for the CIND-induced increase in opioid sensitivity is incompletely understood. CIND preconditions the brain by both directly and indirectly activating intermediate early responsive genes such as c-FOS and c-Jun as well as several transcription factors, including activator protein 1 and hypoxia inducible factor 1 (HIF-1).14 HIF-1, known as the “master regulator,” slowly modulates gene expression for oxygen homoeostasis (including erythropoiesis and angiogenesis) during both continuous or intermittent and acute or chronic

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hypoaxia. Another mechanism is a fast response to hypoaxia, which may be mediated through oxygen-sensing ion channels in specific cells. For both of these responses, several intracellular signaling pathways (including the protein kinases) are involved and may in fact modulate both the fast and slow responses. Unraveling the molecular basis for remodeling opioid receptor signaling during CIND remains one of our major challenges.

Chronic intermittent hypoaxia up-regulates opioid receptor signaling by tipping the balance of excitatory neurokinin-1 and inhibitory μ receptors in favor of the latter. This occurs in part because of hypoaxia-induced endocytosis of the neurokinin-1 receptors. The activity of the μ receptors is further augmented by a transient decrease in the neurokinin-1 receptor binding capacity that occurs after acute hypoaxia. The net effect is a predominance of μ receptors and an increased sensitivity to opioids.

That SDB occurs in children who are scheduled to undergo T&A surgery is widely appreciated, but that it can also occur in children who present for non-T&A surgery is not. Unexpected slow emergence, apnea, and/or respiratory events after extubation and in the postanesthesia care unit after non-T&A surgery may suggest an increased sensitivity to opioids, possibly resulting from OSA and CIND. To identify those at risk for OSA, a history of growth retardation, behavior disturbances, enuresis, and poor school performance, as well as snoring and nocturnal apnea, should be sought preoperatively. As the relation between OSA/CIND and opioid sensitivity becomes firmly established, it is time to insist on more reliable and portable means of quickly and accurately diagnosing those who are and are not at risk for OSA/CIND.

How should anesthesiologists modify their practices in lieu of these findings? When a child presents for T&A surgery with a tentative diagnosis of OSA, it seems prudent to assume the child is at risk for CIND and more sensitive to opioids than usual. After induction of anesthesia, tracheal intubation, and the return of spontaneous ventilation, the carbon dioxide response to surgery and inhalational anesthesia should be carefully monitored. Small incremental doses of an opioid (10–20 μg/kg morphine or 0.2–0.5 μg/kg fentanyl) should be titrated intravenously while the capnogram is observed for apnea. If apnea occurs, either no additional doses or a very small dose of an opioid should be administered before extubation. If apnea does not occur, incremental doses of opioids may be given until a therapeutic response has been achieved. If ventilation is controlled during surgery, testing for an exaggerated response to opioids during surgery is precluded. In this case, a small dose of opioid may be administered during surgery and supplemental doses titrated postoperatively until the pain is controlled. Children with OSA and CIND or those identified as sensitive to opioids should be extubated awake. Postanesthesia care unit and ward staff should be apprised of the child’s sensitivity to opioids and cautioned regarding the dose and frequency of supplemental opioids. Finally, because children with OSA/CIND may obstruct their airways and desaturate on the first posttonsillectomy night, overnight monitoring should include pulse oximetry.

In this issue of the Journal, two studies provide compelling evidence for the judicious use of opioids in children with OSA/CIND as a means of providing adequate analgesia as well as attenuating perioperative respiratory events. By recognizing that SDB and OSA/CIND may occur in children who are scheduled to undergo T&A as well as other types of surgery, and by adjusting opioid doses accordingly, perioperative respiratory events in these children may be obviated.

References

NERVE damage after regional anesthesia is appropriately regarded as a major complication and, when the injury is severe, may take weeks or even months to recover completely.1,2 There are many possible causes for such injuries.3,4 These include stretching, compression, ischemia, surgical trauma, and local anesthetic toxicity.5–7 One causative factor that has been the subject of intense discussion involves the direct intraneural injection of local anesthetics. The deleterious effect of such injections was demonstrated by Selander et al.2 nearly 30 yr ago. Since that time, we have been advised to avoid direct contact between the needle and nerve and to think of the epineurium as a barrier that we should not cross. One consequence of this advice has been a move away from “seeking paresthesias” during the performance of blocks and the use of electrical stimulation and evoked motor responses to estimate proximity to the nerve. However, in this issue of ANESTHESIOLOGY, Dr. Bigeleisen8 has challenged the idea that intraneural injection is uniformly damaging and is to be avoided at all costs.

In this study, videography and ultrasonography were used to assess local anesthetic distribution when axillary brachial plexus block was performed according to his usual practice, which was seeking paresthesia by needle manipulation. When paresthesia was established, 2–3 ml local anesthetic was administered. If the injection appeared intraneurally, the needle was withdrawn until it appeared outside the nerve, the injection was continued, and the block was completed. The patients were checked 6 months later for the occurrence of neuropathy. The results of the study were surprising: 22 of 26 patients (85%) had nerve puncture of at least one nerve, and 21 of 26 patients (81%) had an intraneural injection of at least one nerve. Assessment 6 months later showed no clinical evidence of nerve damage. Two important new considerations emerge from this investigation: First, intraneural injection of local anesthetic, at least in a small volume, does not seem to result in nerve damage, and second, performance of the paresthesia technique does result in frequent intraneural injection.

The belief that administration of local anesthetic inside the epineurium uniformly results in nerve damage should be reconsidered in view of Bigeleisen’s results.8 The study showed that injection of local anesthetic (2–3 ml) inside the epineurium does not result in severe nerve damage. Some minor, transient neurologic symptoms may have occurred between block performance and neurologic assessment at 6 months and may have been unrecognized, but the occurrence of severe nerve damage would most likely have been brought to the attention of the author or detected by the surgeon.

Ultrasonographic resolution does not allow us to differentiate between an injection into the subepineurium or subperineurium. The perineurium, in contrast to the epineurium, is a tough and resistant tissue withstanding very high pressure.5 The ability to expand the nerve, as shown in figure 2B in Bigeleisen’s article,8 suggests that the needle lies in a compliant space between the epineurium and perineurium. However, the main issue coming from this investigation is that the barrier that should not be penetrated to avoid severe neural damage is likely the perineurium. The next question, which cannot be answered, is how much volume can be placed in this space until the pressure increases and adversely affects the blood supply. A study will be needed to clarify this question.

A more recent study by Hadzic et al.9 further evaluated the consequences of either subepineurium or subperineurium injections in dogs. In this study, the authors placed the tip of the needle under microscopic control either around the epineurium or intraneurally by piercing the epineurium. In the control group, injection pressures were low (< 4 psi) in all animals. In the intraneural group, the authors were able to distinguish two subgroups: one with a moderately increased injection pressure, and the other with a very high injection pressure (25–45 psi). After the dogs awakened from general an-
esthersia, motor function returned to normal within 3 h in all animals, except for those with very high injection pressures. In this subgroup, severe and persistent motor deficits were recorded, with varying degrees of damage to the neural architecture. The weakness of this investigation resides in the absence of proof that the needle was effectively placed subperineurally. Similar studies using electronic microscopy and injection of dye should be able to confirm these suppositions.

Another interesting point made by Bigeleisen8 is the apparent high frequency of subepineurium local anesthetic deposition when using the paresthesia technique for performing peripheral nerve block. These findings give support to those promoting the use of electrical nerve stimulation. However, the volume of the injection that enters subepineurally is unknown in this context, but this observation may explain the greater incidence of minor neurologic symptoms observed by some authors using the paresthesia technique10 and the observation that the incidence of severe neurologic complication is not greater when using the paresthesia technique compared with electrical nerve stimulation.10 Therefore, intraneural injection may not cause severe neurologic deficits and might be explained by the relatively good tolerance of low or moderate volume of local anesthetics between the epineurium and perineurium. Another interesting finding reported by Bigeleisen8 is the heterogeneous description of symptoms observed after eliciting paresthesia—a phenomenon that is poorly explained. It must be emphasized that the possibility to “contact” the nerve without eliciting any paresthesia or dysesthesia may occur. This phenomenon has occasionally been reported in the literature.11

This investigation has some limitations. Detractors will criticize the current study because of its relatively small sample size and the lack of any neurologic assessment until 6 months after the injection. It has been demonstrated that most peripheral nerve injuries are transient after regional blocks and resolve within a few weeks after the injury.1,2 However, this study raises pertinent questions about the importance of penetrating the epineurium and nerve damage during regional anesthesia.

In summary, for neurologic complications from regional anesthesia, the belief that the epineurium as the last barrier should be balanced—local anesthetics should be injected outside of it—but we should recognize that some local anesthetics can be injected without uniformly damaging the nerve. Evidence is growing that the key barrier is the perineurium. The work performed by Bigeleisen8 contributes to this understanding. However, this new information should not yet change our clinical practice: Nerves should be treated with care, and the basic rule not to inject local anesthetics into the nerve remains.

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