The letter by Chelly[1] reminds us that we are perioperative physicians and that optimal postoperative analgesia might begin with a preoperative intervention. Addressing psychological factors linked to pain and elevated analgesic requirements is suggested, proposing complementary strategies such as acupuncture, music therapy and others. We agree that any potential opportunity for early intervention is not to be squandered, although preemptive analgesia has not been conceptually substantiated. The general call to address pain management comprehensively is important. Caution is suggested, however, in placing too much faith in strategies that currently have relatively little data supporting them.

Forget *et al.*[2] provide a more extensive set of concerns over some of the particulars of the opioid-free dexmedetomidine anesthetic investigated by Beloeil *et al.*[4] Regrettably, Forget *et al.* "strongly disagree" that opioid-free anesthesia can do more harm than good, despite the study by Beloeil *et al.* being stopped early over major safety concerns (five episodes of bradycardia and three cases of asystole in the opioid-free dexmedetomidine group). We do agree, however, that safer and perhaps more effective protocols could potentially be designed, but they must also be rigorously tested and show benefit to patients. Such benefit must not be limited to intermediate outcomes of opioid consumption but also extend to more important, patient-centric outcomes, including pain, adverse events, recovery, function, and quality of life.[7] We reiterate the thrust of our editorial comments, which were that balance may be the best approach to anesthetic and analgesic management rather than fashion, dogma, or the challenging concept that powerful opioid analgesics should be eliminated as a class for no particularly compelling reason.

Finally, Ingrande and Drummond[3] succinctly comment on the lack of evidence supporting the sometimes-bewildering combinations of analgesics and adjuncts used in the name of eliminating opioids. They point out that the downsides of poorly evaluated but aggressive multi-modal analgesic strategies might be unexpected drug interactions and unclear safety profiles. The point is well taken.

Research Support

This work was supported by National Institutes of Health grant No. R01 DA042985 (Bethesda, Maryland; to Dr. Kharasch) and Department of Veterans Affairs grant No. I01 BX000881 (Washington, D.C.; to Dr. Clark).

Competing Interests

Dr. Clark has a consulting agreement with Teikoku Pharma USA (San Jose, California). Dr. Kharasch declares no competing interests.

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DOI: 10.1097/ALN.0000000000003912

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(Accepted for publication July 6, 2021. Published online first on August 13, 2021.)

Perioperative Stroke: Comment

To the Editor:

The review by Vlisides and Moore[1] did not mention a recently identified group of genetic disorders posing a significant risk for stroke, the most common of which is CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy).[2,3] CADASIL is caused by an autosomal dominant defect in the *NOTCH3* gene, causing abnormal, fragile vascular smooth muscle and resulting in early stroke and dementia in a genetic pattern similar to Huntington disease: 1 per 10,000 prevalence with 50% of offspring affected in mid-adulthood. Although a large hospital will likely encounter several

CADASIL patients each year, the disease is rarely diagnosed or reported.[4]

CADASIL is readily identified by the history, and so I have added two questions to my preoperative questionnaire: "Do you have blood relatives with stroke and dementia before the age of 60?" (positive in 85% of CADASIL patients), and "Do you have adult-onset migraine headaches with aura?" (positive in 50%).[2] When CADASIL is suspected, a preoperative neurology consult may aid perioperative management. Laboratory studies to confirm the diagnosis include genetic testing, brain MRI showing diffuse white matter disease, and abnormal vasculature observed by skin biopsy or fundoscopic exam. Once the diagnosis is established, no further studies are recommended.[4]

There are no published guidelines on anesthetic management of CADASIL. These patients are at increased risk for stroke, thus performing surgery at a hospital with a stroke unit may be prudent. Project OrphanAnesthesia suggests maintaining "cerebral perfusion pressure through systemic arterial pressure, and volume replacement. If needed, direct vasopressors are preferred, but the indirect ones have been used without problems (low dose). Both hypo- and hypercapnia should be avoided because the limits of autoregulation of the diseased vessels are not known."[4] General anesthesia in the sitting position, which has been associated with decreased cerebral blood flow and rare perioperative strokes,[5] should be used judiciously or avoided. Postoperatively, CADASIL patients should be monitored as described by Vlisides and Moore. Awareness of CADASIL may reduce perioperative morbidity in this vulnerable population.

Competing Interests

The author declares no competing interests.

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DOI: 10.1097/ALN.0000000000003856

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(Accepted for publication May 13, 2021. Published online first on June 24, 2021.)

The corresponding author of the original article referenced above has read the letter and does not have anything to add in a published reply.

Perioperative Stroke: Comment

To the Editor:

THE review article about strokes in surgical patients[1] omitted an important, although rare, cause of strokes. Patients undergoing shoulder surgery in the sitting or beach chair position risk a hypotensive/hypoperfusion ischemic stroke because the mean arterial pressure (MAP) in the brain is significantly lower than the cuff blood pressure measured at the arm (heart level). This intraoperative event is especially devastating because it occurs in relatively healthy patients who usually have no risk factors for stroke; they are simply undergoing shoulder surgery to improve their quality of life.

How does this happen? The beach chair position sits the patient at about 70 degrees. The brainstem MAP is about 20 to 40 mmHg lower (depending on the patient's height) than the measured cuff blood pressure. The additional height to the cerebral cortex lowers brain MAP another 6 to 9 mmHg. Every inch of vertical height from the blood pressure cuff's position on the arm to the brain reduces MAP 2 mmHg.[2] This principle was well understood when anesthetizing neurosurgical patients for sitting craniotomies decades ago; appropriate adjustments were made to maintain adequate MAPs in the brain.[3] This correction seems to have been forgotten or no longer taught. In 2005, a report of four cases called attention to this rare, but tragic, complication of brain death/strokes.[4] In 2009, the Anesthesia Patient Safety Foundation called for more clinical and experimental research.[5] We now better understand the physiologic mechanisms, etiology, prevention, and anesthetic management of this problem.[6]

The lower limit of autoregulation to maintain cerebral blood flow was revised upward from 50 mmHg to 70 to 80 mmHg.[7] When patients are positioned upright under general anesthesia with positive pressure ventilation, blood

pressure usually decreases well below the patient's baseline or preoperative level to MAPs of 60 to 70 mmHg. If these low cuff blood pressures are not restored toward baseline levels and may even drift down further to MAPs in the 40- to 60-mmHg range, cerebral perfusion pressure will be in the 20- to 50-mmHg range.

Therefore, it is critically important, when evaluating the etiology of brain death or stroke in these patients, to account for the gravitational effect on cerebral perfusion pressure in order to include severe hypotension leading to brain damage in the differential diagnosis of the ischemic stroke. Thus, it is recommended that cuff blood pressure be maintained at or near baseline to better protect cerebral perfusion.[6,8,9]

As Drummond states,[10] "We cannot take assurance from the notion that at any given time, 'some' of the brain is not ischemic. It would be slim consolation to the devastated patient or their families to know that blood flow continues to some portions of the nervous system while disabling damage was evolving in others."

Competing Interests

The author declares no competing interests.

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DOI: 10.1097/ALN.0000000000003919

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(Accepted for publication July 9, 2021. Published online first on August 16, 2021.)

The corresponding author of the original article referenced above has read the letter and does not have anything to add in a published reply.

Liposomal Bupivacaine to Treat Postoperative Pain: Comment

To the Editor:

We commend Ilfeld *et al.*[1] for their comprehensive review regarding the clinical effectiveness of liposomal bupivacaine when administered *via* infiltration or peripheral nerve block for postoperative analgesia. Since its approval by the U.S. Food and Drug Administration (Silver Spring, Maryland) in 2011, liposomal bupivacaine has been widely adopted and its clinical applications expanded.[1] In the midst of the opioid epidemic, it is easy to understand how long-acting, nonopioid alternatives like liposomal bupivacaine have been eagerly embraced by many physicians. Along with many regional anesthesiologists, we have remained open to the concept but skeptical of the results. The considerable increase in randomized, controlled trials over the last few years has not only shown that the "evidence fails to support the routine use of liposomal bupivacaine over standard local anesthetics,"[1] but it is also fraught with bias.[1] Not limited to the anesthesiology literature, these negative results have been reproduced in other specialties as well.[2–4]

With high-quality studies and a meta-analysis demonstrating that liposomal bupivacaine is not clinically superior to bupivacaine hydrochloride in pain score or length-of-stay measures,[5] one would expect to see an according decline in purchasing, as the 100-fold increase in the cost of liposomal