Opioid-free Anesthesia: Comment

To the Editor:

We read with interest three recently published articles in which opioid-free anesthesia was discussed.[1–3] However, we would like to address several concerns regarding the scientific discussion of these publications.

Beloeil *et al.*[1] hypothesize that opioid-free anesthesia balanced with dexmedetomidine reduces postoperative opioid-related adverse events compared with balanced anesthetic with remifentanil. The results of this trial showed a greater incidence of serious adverse events, especially hypoxemia and bradycardia, in the dexmedetomidine group. However, the trial just compared remifentanil with dexmedetomidine, with ketamine and intravenous lidocaine in both groups. The use of locoregional analgesia or nonsteroidal anti-inflammatory drugs was excluded. Furthermore, the protocol mentioned that dexmedetomidine dosage should be in the range of 0.4 to 1.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and dose adjustments were based on heart rates of the patients and monitored by analgesia nociception index. However, the reported doses of dexmedetomidine were 1.2 ± 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (mean ± SD). Besides the fact that the absence of loading doses of dexmedetomidine may have led to a slow installation of its effect, and that a continuous infusion till the end of the surgery of a sedative agent with a half-life of more than one hour is debatable, we would like to discuss the validity of conducting a trial on high doses of dexmedetomidine. Looking at the dose distribution, some simulations done by us suggest that as many as 21% of subjects may have received more than the allowable maximum dose according to the study protocol, which may be considered a protocol violation because the drug may have dose-dependent side effects (fig. 1). If true, such a frequent protocol violation denotes, at least, a suboptimal study design precluding any extrapolation to a cautious use of the medication, and at the maximum, an earlier interruption of the trial because of hazardous design. The authors argue that high doses are described in other trials, but the only trial they mention to justify this design (high doses without a bolus) is a trial that used a bolus and infused in total 0.6 ± 0.6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (including the bolus dose).[4] Furthermore, the patients were monitored with analgesia nociception index, but the authors never showed results of this monitoring. Therefore, the Postoperative and Opioid-free Anesthesia (POFA) trial uses a nonsupported drug dosage and may have exposed a significant proportion of their participants to protocol violations. Finally, the trial merely reconfirmed the well-known side effects of high doses of dexmedetomidine. The authors are credited for conducting this trial, but it doesn't reflect responsible opioid-free anesthesia practice and just makes the scientific discussion on opioid-free anesthesia more controversial.[2,3] They have only demonstrated the already well-known side effects of high-dose dexmedetomidine rather than opioid-free anesthesia risk–benefit ratio.

Shanthanna *et al.*[2] critically reviewed perioperative opioid use, especially in view of opioid-sparing *versus* opioid-free strategies. In fact, the authors did not explicitly distinguish between eliminating intraoperative opioids (opioid-free anesthesia) and postoperative opioids (opioid-free analgesia). This lack of distinction may confuse the reader into believing that opioid-free anesthesia may mean elimination of all opioids, including in the postoperative and postdischarge periods. Opioid-free anesthesia is, by definition, referring to anesthesia while the patient is asleep, and nociception has to be considered instead of "pain," an experience that is always associated with consciousness. Consequently, at the end of the surgical procedure or at the recovery ward, opioids might be titrated to effect when indicated. Opioid-free anesthesia has emerged as a new stimulating research perspective and has gained in popularity as a way to enhance early recovery and to spare opioids for the postoperative period.[5] Hence, the goal is not by any way an obligation to eliminate the postoperative opioids where these are useful but rather to improve the clinical outcomes. In randomized controlled trials, one meta-analysis and a large retrospective study, it was shown that opioid-free anesthesia strategies may improve different outcomes.[6,7] In addition, the arguments in favor of the use of locoregional analgesia, but also of ketamine, are supported by a significant body of evidence.[8] Shanthanna *et al.* state that opioid-free strategies, including opioid-free anesthesia, are noble in their cause, do not serve to decrease the risk of persistent opioid use, and distract us from optimizing pain and minimizing realistic long-term harms. This statement seems to be a bit biased or at least opinion based and not supported by any evidence.

In an accompanying editorial, Kharasch and Clark[3] state that medical change is driven by concepts of effectiveness and safety and that these concepts should improve and refine as better data become available. We agree with this statement. However, we strongly disagree with their conclusion that the POFA trial clearly demonstrates that we

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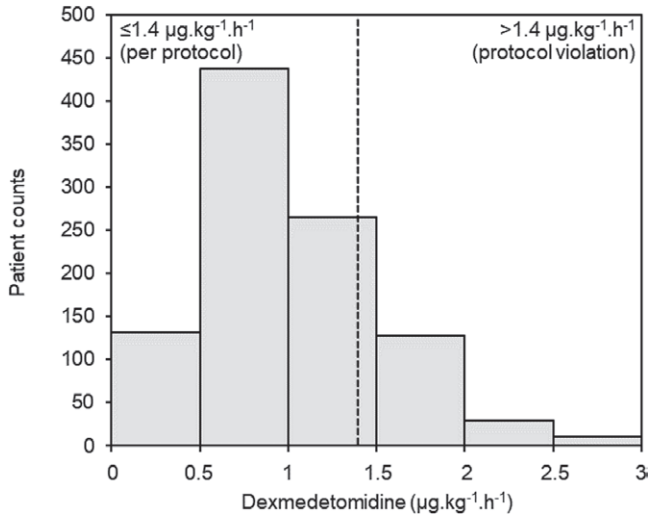

Fig. 1. Dexmedetomidine dose distribution according to a Monte Carlo simulation of a fictive trial with similar data to those of the Postoperative and Opioid-free Anesthesia (POFA) trial with n = 1,000, asymmetric normal distribution, mean ± SD = 1.02 ± 2.0, skewness = 0.89, curtosis = 0.75, dose range: 0.15 to 2.85, patients with a dose greater than 1.4: n = 209.

can do more harm than good by opioid-free anesthesia. The authors never come with scientific data to critically discuss the use of opioids and are opposing opioid-free anesthesia by using the results of the POFA trial without discussing the many limitations of the POFA trial, which doesn't represent proper opioid-free anesthesia practice. It is important to underline that opioid-free anesthesia is not an overreaction to the opioid crisis; opioid-free anesthesia existed before this crisis and started before in the European countries where opioids crisis was not a concern.[5] If we respectfully disagree with the Kharasch and Clark's statement that opioid-free anesthesia may appear neither logical nor beneficial to patients, opioid-free anesthesia could be misapplied in clinical practice. Thus, we do agree that a more critical look should be considered for further evaluation in the next future.

Are opioids really some of our most powerful drugs, as stated by Kharasch and Clark? There are many uncertainties about the pervasive effect of opioids and strong evidence for the existence of dose-dependent toxicity.[9] There are strong arguments that intraoperative opioids, remifentanil in particular, may be associated with worse postoperative pain and worse outcomes, making their safety profile questionable. Moreover, intraoperatively used remifentanil showed unexpected unfavorable outcomes and was associated with a deterioration of pain levels and increased postoperative analgesic requirement.[10] The potential benefits of remifentanil seem to be outweighed by its potential disadvantages, especially in surgical procedures in which high postoperative pain scores are expected.[11] Furthermore, opioid-induced hyperalgesia is induced by higher doses of intraoperative opioids and associated with increased postoperative pain scores and higher morphine consumption.[12] Therefore, for many reasons, opioids are not a holy grail in anesthesia, and their use should be carefully reconsidered.

We stress the importance of proper education regarding how to practice opioid-free anesthesia and how new ways of monitoring of antinociception may help implement opioid-free anesthesia. Furthermore, future well-designed trials that investigate the role of opioid-free techniques in multimodal anesthesia make sense only if they are part of a continuum where the development of patient-centered approaches is essential. The main goal in perioperative medicine is to enhance recovery, reduce complications, and improve outcome, not by focusing on using or not using of opioids (intraoperatively) only but also to broaden our scope in which research and development of opioid-free anesthesia strategy as part of multimodal anesthesia approaches deserves a place, rather than being excluded.

Competing Interests

Dr. Mulier received personal fees, department grants, financial support, and nonfinancial support to organize scientific meetings from MSD Merck (Kenilworth, New Jersey), GE Healthcare (Chicago, Illinois), Medtronic (Dublin, Ireland), and Johnson & Johnson (New Brunswick, New Jersey) outside the submitted work. Dr. Lavand'homme was in the pharmacovigilance committee of the POFA trial and has no other conflict of interest. Dr. De Baerdemaeker has received departmental nonrestricted educational grants from GE and Medtronic. Dr. de Boer has received research grants from

Merck and is member of the Executive Commitee and treasurer of the ERAS Society. The other authors declare no competing interests.

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Opioid-free Anesthesia: Comment

To the Editor:

With increasing frequency, we encounter patients to whom, under the banners of enhanced recovery after surgery and multimodal analgesia, a multitude of drugs have been administered. At times, the melange can include a cyclooxygenase-2 inhibitor, dexamethasone, dexmedetomidine, fentanyl (and/or other opioids), gabapentin, ketamine, lidocaine, midazolam, magnesium, scopolamine (transdermal), and a volatile anesthetic. The recent articles by Beloeil *et al.*, Shanthanna *et al.*, and Kharasch and Clark have all presented timely and clinically pertinent discussions of the analgesic limitations of the multimodal analgesia regimens that have been implemented in the name of opiate sparing and opioid-free anesthesia.[1–3] However, we suspect that the hazards of these regimens have not been given sufficient emphasis. While the enhanced recovery after surgery and multimodal analgesia banners may be worthy ones, and their benefits may be substantial, the potential harms have been underestimated.

The easy observation is that the multitude of potential drug interactions seems to be given little consideration and has most definitely received little systematic study.[4,5] To highlight that point, consider the elaborate detail of our knowledge of the response face interactions of propofol and opioids and contrast that with the void that is our systematic knowledge of the interactions between the various agents administered during multimodal analgesia. Second, the zeal

to pursue multimodal analgesia has led to the implementation of drugs, most notably lidocaine and ketamine, whose efficacies, ideal situations, and optimal regimens (if they are effective at all) are more dependent on speculation and best guess than science.[6–8]

There is no question that opioids remain the most efficacious analgesics available. For the better part of the last half century, opioids have been a pillar of balanced anesthesia. Coupled with our sedative-hypnotics, opioids interact synergistically to increase sedation and control autonomic nervous system responses. These interactions are known and indisputable—response surface models describe this synergism specifically and elegantly.[9,10] This two-drug, balanced anesthetic is simple, reliable, and scientifically sound.

In and of themselves, nonopioid analgesics do not have the same efficacy as opioids. One by one, the utility of these drugs as perioperative analgesics is being disproven as studies hypothesizing their efficacy are prematurely halted for futility.[1,11]

Undeterred by the lack of efficacy of single nonopioid drug regimens, proponents of nonopioid analgesia have employed various combinations of these drugs, in varying concentrations, in the hope that additive or synergistic interactions will result in a clinical effect equal to that of opioids. Unfortunately, the exact nature of the interactions between nonopioid analgesics is poorly characterized.[12] To date, there are no well-characterized, evidenced-based, opioid-free regimens to serve as guides for clinical application.[13] In fact, many regimens are anecdote-based "recipes" employing a variety of combinations and doses.[14–16] Uncharacterized interindividual variability in the relationships between drug concentration over time (pharmacokinetics) and physiologic response *versus* drug concentration (pharmacodynamics) has made rational selection of agents and dosing regimens difficult. Simply stated, we know very little to nothing about proper drug combinations or dosing regimens.

To ignore the potential harm of the polypharmacy associated with multimodal analgesia is hubristic. It is naive to assume that the side effects of these agents are benign or less severe than those of opioids.[1,17–21] Furthermore, there is clear evidence that the incidence of adverse drug–drug interactions increases exponentially with the number of drugs administered. Approximately 40% of patients given 16 drugs during an anesthetic had an adverse drug interaction, compared to only 5% who were given 6 drugs.[22,23]

The promises of multimodal analgesia are grand: provide analgesia equal to that offered by opioids with a side-effect profile that is comparably benign. Unfortunately, the side effects of these drugs are not benign, the analgesic efficacy of various combinations is unproven, and the optimal combinations and doses remain speculative or anecdote-based at best. Furthermore, as separate groups of well-intentioned care providers work in parallel to implement both enhanced recovery after surgery and multimodal analgesia strategies, the potential for drug interactions to intrude is further increased. To our habit of "Vigilance," we should add caution and skepticism about incompletely studied drugs and drug combinations.

Competing Interests

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To the Editor:

Beloeil *et al.*[1] present a compelling pragmatic trial comparing dexmedetomidine with remifentanil in a balanced anesthetic. We congratulate them on executing such a challenging trial and reinforcing that "opioid-free" is not "complication-free." Their work raises important questions about the future of balanced anesthetics, especially the use of non-opioid infusions. Although the authors primarily compared a dexmedetomidine infusion (to make it "opioid-free") with a remifentanil infusion, their underlying anesthetic also included ketamine and lidocaine infusions. Of these infusions, we are concerned about the ubiquitous use of intravenous lidocaine for assumed benefit without regard to risk.

Intravenous lidocaine is fashionable for its analgesic properties in the opioid-sparing epoch.[2] Given the high median lethal dose, short half-life, and rapid dissociation from voltage-gated sodium channels, most practitioners believe that lidocaine infusions are benign. However, clinicians have reported life-threatening events associated with lidocaine infusions for more than 40 yr and continue to do so.[3] Further, lidocaine alone (16 cases) or in combination with other local anesthetics (8 cases) was implicated in a majority of 36 case reports of local anesthetic systemic toxicity between December 2017 and May 2020, including one lidocaine-precipitated fatality.[4] Lidocaine infusions may have a large therapeutic index in healthy patients but less so in those who are elderly, are frail, and have systemic comorbidities. In particular, cardiac disease, liver disease, hypoalbuminemia, and other severe systemic diseases will compromise lidocaine clearance, necessitating dose reductions.[5,6]

As a case in point, Beloeil *et al.* report a case of severe local anesthetic systemic toxicity in a 44-kg patient

presenting for open pancreatic surgery that resulted in asystole and required intravenous lipid emulsion. Beloeil *et al.* justify their use of lidocaine by asserting that it "reflects some common practices based on international literature."[1] However, the referenced systematic review[7] specifically stipulates the risk of bradycardia and arrythmia from intravenous lidocaine infusions. Further, the majority of the trials in that systematic review excluded patients with severe systemic disease that would put patients at risk for lidocaine accumulation and toxicity. We recognize the complexity of the trial design and do not wish to diminish the importance of the current work. However, the case of bradycardic arrest should not only give us pause about the safety of dexmedetomidine infusions; it also provides an opportunity to discuss appropriate use of lidocaine infusions in patients with severe systemic disease.

Competing Interests

The authors declare no competing interests.

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Opioid-free Anesthesia: Comment

To the Editor:

I read with great interest the editorial from Kharasch and Clark, titled "Opioid-free Anesthesia: Time to Regain Our Balance."[1] However, after reading the editorial, I am still unclear on why we need such a discussion in the context of Beloeil *et al.*'s study.[2] Opioid-free anesthesia is not just about replacing an opioid with a nonopioid analgesic. Maybe in the United States the use of opioids is more concerning because it is established that 80% of the world opioid consumption occurs in the United States. In my opinion, the real question is: Do we need opioids to optimize perioperative care and recovery of a surgical patient? Although Shanthanna *et al.*[3] provide evidence that opioids are not always required if patients are properly selected and regional anesthesia and complementary techniques are included, consideration should also be given to the role that anesthesiologists may have in perioperative medicine, which, in the case of perioperative pain and opioid requirement, includes their role in the patient preparation for surgery.[4] For example, increasing evidence demonstrates that preoperative anxiety, depression, and/or catastrophizing are factors that may increase up to 50% postoperative pain and opioid requirements.[5] What makes mood disorders so interesting to consider is that, if identified preoperatively, their effects on postoperative pain and opioid requirements can be "normalized." Also, as a specialty, we seem to minimize the role of complementary and alternative techniques that, when applied preoperatively, have been shown to reduce

perioperative pain and opioid requirements. Examples include acupuncture, music therapy, auriculotherapy,[6] aromatherapy, and hypnosis.[7]

Opioid-free anesthesia is not about replacing opioids with other analgesics. In many ways, it illustrates what we can achieve as a specialty if we apply a more comprehensive approach to perioperative pain management and opioid requirement.

Competing Interests

The author declares no competing interests.

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Opioid-free Anesthesia: Reply

In Reply:

We appreciate Forget *et al.*,[1] Ingrande and Drummond,[2] and Fettiplace and Gitman[3] for their interest in our work.[4] As noticed by the authors, we chose to not administer a nonsteroidal anti-inflammatory drug to facilitate the recruitment of patients in the study. However, we agree that nonsteroidal anti-inflammatory drugs should be administered whenever possible. We also chose to not administer regional anesthesia in patients included in the Postoperative and Opioid-free Anesthesia (POFA) study because they were already receiving intravenous lidocaine. Another study replacing intravenous lidocaine by regional anesthesia would, of course, be of interest. It was perhaps not clearly stated in our article, but the dosage of dexmedetomidine was adapted not according to the Analgesia Nociception Index but rather according to the patient's heart rate. This was decided in the original design[5] because of the lack of validation of the Analgesia Nociception Index during opioid-free anesthesia. Concerning the doses of dexmedetomidine, 14.3% of the patients received a dose higher than 1.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and not 21% as stated by the simulation made by the authors. Moreover, as also already stated, complications were analyzed according the dosage of dexmedetomidine (lower or higher than the median value of the whole population: 0.9 $\mu g \cdot kg^{-1} \cdot h^{-1}$), and no differences were observed, including for bradycardia. To answer to the authors' critics, we also performed a complementary analysis of the primary endpoint in the subgroup of the patients who received dexmedetomidine with a dosage within the predefined range (0.4 to 1.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$). The results were similar with the occurrence of the composite primary endpoint being 64% in the opioid-based anesthesia group and 77% in the opioid-free anesthesia group and occurrence of hypoxemia being 61% and 74%, respectively. Finally, we wonder what is the "responsible opioid-free anesthesia practice" proposed by the authors. So far, no study has been published on the optimal dosage of dexmedetomidine during opioid-free anesthesia or on an evidence-based opioid-free regimen.

We fundamentally agree with Ingrande and Drummond's[2] statement on the need to study the nature of the interactions between all the analgesics we are using in daily practice. We also agree that there is no well-characterized, evidence-based opioid-free regimen, and there is an urgent need to study the implications of the actual opioid-free anesthesia trend among anesthesiologists. Our study was an attempt to further study these drug-to-drug interactions.

We agree on the risk associated with intravenous lidocaine, as noted by Fettiplace and Gitman.[3] However, in our study, the case presented was not a case of local anesthetic systemic toxicity. The patient experienced a severe bradycardia and asystolia after an overdosage of dexmedetomidine as a result of an overestimation of the patient's weight. Intravenous intralipids were systematically administered because the patient received intravenous lidocaine. However, the *post hoc* analysis of the case concluded that it was an overdosage of dexmedetomidine and not the consequences of local anesthetic systemic toxicity.

Competing Interests

Dr. Beloeil reports receiving fees as a speaker (AbbVie [Lake Bluff, Illinois], Aspen [Durban, South Africa]) and as member of an expert board (Orion Pharma, Espoo, Finland). The other authors declare no competing interests.

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In Reply:

We thank Forget *et al.*[1] and Ingrande and Drummond[2] for their interest in our review on perioperative opioid administration.[3] Forget *et al.* contend that we did not distinguish between opioid-free anesthesia and opioid-free analgesia and ignored published studies and a meta-analysis.[4] On the contrary, we explicitly distinguish between these two phases of care and even abbreviate them, so as to clarify our position throughout. Unfortunately, the definition of opioid-free anesthesia in literature seems to be loosely applied and consequentially misinterpreted. Whether opioid-free anesthesia means total abstinence or relative lack of intraoperative opioids is unclear. We discuss this as an important limitation of the review and meta-analysis by Frauenknecht *et al.*,[4] in which included studies used opioids during the intraoperative period, thereby resulting in a potentially inappropriate conclusion.[5] Furthermore, our statement that total avoidance of perioperative opioids has no influence on the long-term outcomes is based on evidence,[6–8] contrary to the statement made by Forget *et al.*[1] The most fundamental question is whether the goal of total opioid avoidance is really necessary and at what cost.

Ingrande and Drummond[2] draw attention to the fact that use of combination of medications (polypharmacy) is hazardous, which is indeed true. However, with regard to multimodal analgesia, we differ from their broad interpretation. The original definition of multimodal analgesia clarifies that the goal was to achieve sufficient analgesia due to synergistic effects between different group of analgesics, with accompanying reduction of side effects as one would be less dependent on a single analgesic modality.[9] In our article, we clarify that the choice of what can be included

as multimodal needs to be based on (1) intrinsic analgesic potency, (2) opioid-sparing potential, and (3) potential side effects. Bundling all modalities under nonopioid analgesics is inappropriate. We need to distinguish between adjuncts such as gabapentinoids, dexmedetomidine, lidocaine, ketamine, and magnesium *versus* known analgesics such as acetaminophen, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2–specific inhibitors or loco-regional techniques.[10] In fact, acetaminophen and nonsteroidal anti-inflammatory drugs or cyclooxygenase-2–specific inhibitors should be administered to all surgical patients unless there are contraindications.[10] Moreover, there are procedure-specific and patient-specific considerations, and a one-size-fits-all approach is not recommended. Because avoiding opioids, irrespective of the context, is seen to provide a compelling narrative in the background of the opioid crisis, analgesic practices seem to have resorted to multiple combinations of untested agents, overzealous application of drug combinations, or multiple interventions leading to toxicity and patient harms.[11,12] We highlight the need for more balanced and responsible decision-making.

Competing Interests

Dr. Joshi has received honoraria from Baxter International Inc (Deerfield, Illinois) and Pacira Bioscience Inc (Parsippany, New Jersey). The other authors declare no competing interests.

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Opioid-free Anesthesia: Reply

In Reply:

It serves as evidence of compassionate concern for patients and dedication to improving practice that several letters[1–3] were received in response to the articles by Beloeil *et al.*[4] and Shanthanna *et al.*[5] on opioid-free anesthesia, and to our accompanying editorial.[6] The topic of opioid-free anesthesia is one of intense interest to the field, and these articles are commended to the reader. Those points made in the letters specific to our editorial are addressed briefly below.

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.

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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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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