The Potential Role of $\alpha_2$ Agonists for Noncardiac Surgery

Acute pain after noncardiac surgery provokes suffering, activates the sympathetic nervous system which augments myocardial demand, delays mobilization and recovery, and may result in chronic postoperative pain. Although the last 50 yr have witnessed advances in the prevention and management of acute pain after noncardiac surgery (e.g., acute pain services, patient-controlled analgesia), postoperative pain remains common. Physicians regularly use opioids to prevent and manage acute postoperative pain. Many authors have advocated multimodal analgesia with the goal of sparing opioid use and thus presumably reducing potential opioid-related adverse effects, including respiratory depression, hypotension, nausea and vomiting, bradycardia, delirium, hypothermia, hyperalgesia, immune system compromise, and constipation. In this issue of Anesthesiology, Blaudszun and colleagues present a systematic review and meta-analyses of randomized controlled trials addressing the important topic of whether systemic $\alpha_2$ agonists reduce postoperative opioid use and improve pain control in patients having noncardiac surgery. This systematic review included 1,792 randomized patients from 30 trials, of which 19 evaluated clonidine and 11 evaluated dexmedetomidine.

Meta-analyses by Blaudszun and colleagues demonstrated that clonidine administration reduced average postoperative cumulative morphine equivalents by 9.8 mg at 12 h and 4.1 mg at 24 h. Meta-analyses also demonstrated that dexmedetomidine administration reduced postoperative average cumulative morphine equivalents by 6.0 mg at 12 h and 14.5 mg at 24 h. What represents a clinically important decrease in opioid sparing after noncardiac surgery? One answer is the dose that reduces opioid-related adverse effects. The investigators demonstrated that clonidine and dexmedetomidine reduced postoperative nausea but not vomiting. Other potential opioid-sparing effects were not reported, including respiratory depression, delirium, hypothermia, hyperalgesia, and immune system compromise.

Meta-analyses by Blaudszun and colleagues demonstrated that clonidine administration reduced postoperative pain scores (on a 10-cm visual analog scale) by 1.5 cm at 12 h and 0.7 cm at 24 h. Meta-analyses demonstrated that dexmedetomidine administration reduced postoperative pain scores by 1.4 cm at 1 h and 0.6 cm at 24 h. What represents a clinically important change in pain scores using a visual analog scale? Studies suggest that decreases in individual pain scores of 1 cm represent minimal or little change, whereas decreases of 2 cm or more represent a substantial reduction in pain that can result in a decreased need for rescue pain-relief medication.

However, what represents an important change in an individual’s pain score differs from what represents an important difference between group pain scores.

Unfortunately, the $\alpha_2$ agonist data are reported only as differences between group scores, rather than the percentage of patients in each treatment group who experienced a clinically important change being reported. Despite this limitation, it is possible, and considering the differences between group pain scores and the opioid sparing-effects, perhaps even probable, that $\alpha_2$ agonists resulted in an appreciable relative increase in the number of patients experiencing a clinically important reduction in their pain scores.

An alternative method for assessing the effect of $\alpha_2$ agonists on opioid sparing and pain scores is to compare their impact to that of other drugs. Blaudszun and colleagues compare their results to other meta-analyses and suggest $\alpha_2$ agonists provide greater morphine and pain-sparing effects than...
does acetaminophen but less than that of ketamine or non-steroidal antiinflammatory medications. This sort of non-systematic indirect comparison must be considered with caution because it cannot exclude chance as a potential explanation of any apparent differences. At a minimum, a network meta-analysis for indirect comparisons is required, and ideally, a trial of direct comparisons is needed to inform such questions.

Another relevant point that readers should consider when interpreting this systematic review is that, although overall nearly 1,800 patients in 30 trials were considered, most reported outcomes were based on meta-analyses that included only three to five trials and typically a total of 100–400 patients. Although many epidemiologists place meta-analyses at the top of the hierarchy of evidence pyramid, physicians should view the results of meta-analyses with healthy skepticism when they include only small trials. The results of large trials are almost always published or available, but many small trials are not, for various reasons, including loss of interest on the part of the investigators and challenges with trying to publish neutral results. The difficulty is that investigators conducting a systematic review typically do not know about the unpublished trials, which potentially biases the results. Unfortunately, our ability to assess for publication bias is generally low and is almost nonexistent when only a few trials are included in a meta-analysis (e.g., the meta-analyses by Blaudszun and colleagues typically included three to five trials). Experts recommend not evaluating publication bias in meta-analyses that include 10 or fewer trials because the tests to assess publication bias are not reliable in this situation. Although trial registration with details regarding the protocol and preplanned analyses have substantial potential to overcome the issue of publication bias and selective outcome reporting, research demonstrates that small trials tend to have lower methodologic quality, larger treatment effects, and more commonly statistically significant results compared with large trials.

Meta-analyses by Blaudszun and colleagues demonstrated that clonidine increased intraoperative and postoperative hypotension (risk ratios, 4.75; 95% CI, 2.17–10.43 and 3.37; 95% CI, 1.27–8.92, respectively). The impact of dexmedetomidine on hypotension was not reported, but it was associated with an increase in postoperative bradycardia (risk ratio, 17.0; 95% CI, 2.35–123.10). Perioperative interventions can have unintended consequences. For example, a large international trial demonstrated that a β blocker reduced the risk of perioperative myocardial infarction but increased the risk of stroke and death. These unanticipated consequences appeared to have occurred primarily as a result of clinically important hypotension. The fragmented nature of physician involvement in perioperative care (e.g., anesthesiologist involvement confined to the operating and postanesthetic care unit, internist involvement confined to preoperative assessment) contributes to the risk of physicians not completely appreciating the full consequences of interventions they initiate, especially when interventions involve long-acting drugs that may have various clinical effects (or effect magnitude), depending on patient care environments. These points highlight why, when assessing the impact of any perioperative intervention, it is important to undertake large trials that consider all relevant patient-important outcomes to at least 30 days after noncardiac surgery.

The systematic review by Blaudszun and colleagues offers encouraging evidence that α₂ agonists may reduce opioid usage and pain scores after noncardiac surgery. However, their results also suggest that perioperative α₂ agonists increase the risk of clinically important hypotension and bradycardia. Although a larger meta-analysis suggests low-dose perioperative clonidine does not increase the risk of clinically important hypotension, the results of the meta-analyses by Blaudszun highlight the need for large trials to evaluate the impact of α₂ agonists on all patient-important outcomes. Fortunately, one is in progress.

A large international group of anesthesiologists, cardiologists, internists, and surgeons are collaborating on the POISE-2 Trial, a 10,000-patient, blinded, factorial randomized controlled trial evaluating the impact of low-dose clonidine versus placebo and low-dose acetyl-salicylic acid versus placebo in adults undergoing noncardiac surgery (NCT01082874). The primary outcome is all-cause mortality and nonfatal myocardial infarction at 30 days after surgery. The trial also will evaluate various vascular (e.g., stroke) and renal (e.g., acute kidney injury) outcomes, along with the effect of clonidine on chronic postoperative pain a year after surgery. This trial has already recruited more than 3,500 patients and should complete recruitment within another 2 yr.

α₂ Agonists have many attractive properties, including enhanced perioperative pain control, which suggest that patients having noncardiac surgery may benefit from these agents. However, previous large trials remind us that physiologic and surrogate endpoints may not inform patient-important outcomes. Large trials such as POISE-2 will help clarify the role of α₂ agonists in patients undergoing noncardiac surgery.

The systematic review by Blaudszun and colleagues evaluated pain, which is an important perioperative outcome that has received inadequate attention in large clinical trials. Their work offers hope that α₂ agonists may improve acute pain scores and minimize opioid usage and that these outcomes may have an impact on other important outcomes (e.g., chronic postoperative pain). Definitive results await larger trials.

P. J. Devereaux, M.D., Ph.D.,* Daniel I. Sessler, M.D.†
*Departments of Clinical Epidemiology and Biostatistics and Medicine, McMaster University, Hamilton, Ontario, Canada, and Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, Ontario, Canada. philipj@mcmaster.ca. †Population Health Research Institute, and Department of Outcomes Research, Cleveland Clinic, Cleveland, Ohio.
References


