

Steroids to Ameliorate Postoperative Pain

CME

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SURGICAL tissue injury provokes a neuroendocrine stress response and inflammation.^{1,2} The neuroendocrine response can be moderated by regional or neuraxial anesthesia.^{3,4} However, the inflammatory response results largely from local release of mediators that then act systemically.⁵ It is widely believed that the inflammatory response to surgical tissue injury is responsible for serious complications including prolonged fatigue,⁶ atrial fibrillation,⁷ delirium,⁸ and prolonged intensive care unit stay.⁹ It is also likely that inflammation contributes to acute postoperative pain.¹⁰ A variety of antiinflammatory medications including lidocaine,¹¹ selective cyclooxygenase-2 inhibitors,¹² and other nonsteroidal antiinflammatory drugs¹² have thus been used in attempts to reduce surgical pain. The ultimate antiinflammatory drugs, however, are steroids. To the extent that inflammatory mechanisms contribute to postoperative pain, one might expect that preoperative or intraoperative steroid administration would ameliorate postoperative pain. Consistent with this theory, steroids peripherally inhibit phospholipase, thereby decreasing pain-aggravating products of the cyclooxygenase and lipoxigenase pathways.¹³ Corticosteroids also inhibit expression of cytokine genes and release of proinflammatory enzymes, bradykinin, and neuropeptides from injured nerve terminals^{14–16}—all of which also worsen pain. In addition, corticosteroids decrease perioperative proinflammatory mediators including interleukins 1, 6, and 8, along with tumor necrosis factor, C-reactive protein, and leukocyte adhesion molecules.^{15,17} As might thus be expected, many studies have evaluated the effects of steroid administration on surgical pain. In this issue of ANESTHESIOLOGY, De Oliveira *et al.*¹⁸ present a meta-analysis of studies that evaluated the effect of intravenous dexamethasone on postoperative pain.



“... dexamethasone ameliorates acute postoperative pain ... [but] what remains unclear is the risk-benefit ratio.”

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The strength of the analysis by De Oliveira *et al.* is that it evaluates a wide range of doses. Their analysis suggests that higher doses of dexamethasone (more than 0.2 mg/kg) do not improve analgesia compared with medium or low doses. Less clear is whether medium doses are superior to low doses (less than 0.1 mg/kg). A typical 4-mg dose for prophylaxis of postoperative nausea and vomiting¹⁹ thus may or may not be sufficient.

De Oliveira *et al.* also evaluated the effect of timing on postoperative pain. Unlike with most analgesics, many effects of corticosteroids require gene expression and protein production—and thus have a delayed onset. As might be expected, preoperative dosing appeared more effective than intraoperative administration. Edema and inflammation induced by surgery usually persist for days, far longer than the antiinflammatory effect of a single dose of dexamethasone. It is thus somewhat surprising that no studies evaluate the analgesic effect of repeated steroid doses. Persistent incisional pain (lasting longer than 3 months) is common especially after thoracotomy,²⁰ hysterectomy,²¹ and breast surgery.²² Persistent incisional pain is often preceded by severe perioperative pain,²³ suggesting that effective postoperative analgesia may help prevent conversion of acute pain to chronic pain. However, the potential effect of steroids on persistent incisional pain remains unknown.

Increasing evidence suggests that perioperative steroids provide short-term benefits. For example, it is beyond question that low-dose dexamethasone reduces postoperative nausea and vomiting.^{19,24} Similarly, steroids reduce fatigue in the days after surgery.⁶ The meta-analysis by De Oliveira *et al.*¹⁸ provides considerable support for an analgesic effect of steroids. The difficulty is that the same basic antiinflammatory mechanisms that presumably provide these benefits may aggravate risk of surgical wound infection.

◆ This Editorial View accompanies the following article: De Oliveira Jr GS, Almeida MD, Benzon HT, McCarthy RJ: Perioperative single dose systemic dexamethasone for postoperative pain: A meta-analysis of randomized controlled trials. ANESTHESIOLOGY 2011; 115:575–88.

The potential risk of administering perioperative steroids is far from trivial: surgical site infection remains a common and serious complication.²⁵ Furthermore, the transition from inevitable wound contamination to clinical infection occurs during a brief “decisive period” during and for several hours after surgery — and is thought to mostly depend on failure of immune defenses.²⁶ Clinicians thus need to seriously consider potential harm that could result from administration of drugs that specifically impair immune defenses during the decisive period.

De Oliveira *et al.* conclude that “a single dose of perioperative dexamethasone does not increase dose-limiting complications such as wound infection.” However, this conclusion is based on reported infections in the underlying studies included in their analysis; reliance on these studies is a critical limitation because none used appropriate methodology to evaluate infection or was powered to detect clinically important increases in infection risk. A more accurate statement might be that the effect of perioperative steroid administration on wound infection risk remains unknown — and could well be substantial.

Hyperglycemia is another steroid-induced complication. The increase is modest²⁷ but has yet to be well characterized. Furthermore, there is little convincing evidence that small increases in perioperative plasma glucose concentration worsen outcomes.²⁸ At least in most patients, it thus seems unlikely that hyperglycemia is a compelling reason to avoid giving low- to moderate-dose steroids.

The analysis by De Oliveira *et al.* is certainly the most thorough quantitative literature review of perioperative dexamethasone for pain. However, all meta-analyses share basic limitations. A major concern is publication bias, which results from the tendency for positive studies to be published more often than negative ones. Although the authors used statistical methods to evaluate and limit the effects of publication bias, some unknown amount surely remains. Another major issue is the quality of available studies; a meta-analysis is only as good as the underlying studies. For example, pain and/or opioid consumption was not always the primary outcome of the underlying studies; consequently, it was not necessarily well evaluated. This is even more the case for potential steroid-induced complications that were never the primary outcome and thus inadequately evaluated.

In summary, the meta-analysis of De Oliveira *et al.* provides good evidence that dexamethasone ameliorates acute postoperative pain. Whether a low dose (less than 0.1 mg/kg) is sufficient remains unclear, but a dose exceeding 0.2 mg/kg does not appear necessary. The meta-analysis also shows that analgesia is enhanced when steroids are given preoperatively or at least shortly after induction. What remains unclear is the risk-benefit ratio because the underlying studies did not adequately evaluate the potential substantial effect of steroids on host resistance to the bacteria that cause surgical site infections.

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ANESTHESIOLOGY REFLECTIONS

Block-ing Pain with Jiffy Toothache Drops



Founded in Brooklyn, New York, in 1907 by Lithuanian-American pharmacist Alexander Block, the Block Drug Company shifted its headquarters in 1938 to nearby Jersey City, New Jersey. From there it produced or distributed dozens of products, including “Jiffy Toothache Drops” (above) which featured a topical anesthetic blend of benzocaine, eugenol, and menthol. (Of course the accompanying mix of chloroform in “54.2% Alcohol” also helped relieve dental pain in a “Jiffy” . . .) After the founder’s death in 1953, Block Drug was run by his family, then traded publicly from 1971–2001, and finally sold to a pharmaceutical giant. (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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