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Glucocorticoids for Acute and Persistent Postoperative Neuropathic Pain

What Is the Evidence?

PERSISTENT neuropathic postoperative pain is a major health problem. It is highly important to find therapies that prevent or reduce chronic neuropathic postoperative pain. The current issue of ANESTHESIOLOGY contains an animal study by Li *et al.*[1] that examines the role of a systemic glucocorticoid (triamcinolone acetonide) on aspects of pain and inflammation using the spinal nerve ligation model. This model is traditionally considered a neuropathic pain model, but involves surgery and evokes an inflammatory response linked to pain behavior. In their study, Li *et al.*[1] demonstrate that systemic injections of a glucocorticoid reduce apparent pain behavior, proinflammatory cytokines, overall neuronal firing rate, incidence of bursting activity, and abnormal sympathetic sprouting in dorsal root ganglia.

Proinflammatory cytokines secreted at or near the site of a nerve injury are involved in the development and maintenance of central sensitization and neuropathic pain.[2,3] Glucocorticoids suppress proinflammatory cytokines and induce expression of antiinflammatory cytokines.[1,2,4–6] They also reduce the prostaglandin synthesis by inhibiting phospholipase A_2 and by blocking the expression of cyclooxygenase-2 messenger RNA.[4,6]

This Editorial View accompanies the following article: Li W, Xie W, Strong JA, Zhang J-M: Systemic antiinflammatory corticosteroid reduces mechanical pain behavior, sympathetic sprouting, and elevation of proinflammatory cytokines in a rat model of neuropathic pain. ANESTHESIOLOGY 2007; 107:469–77.

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Spinal glial activation stimulates nuclear factor κB, which induces cyclooxygenase-2, release of prostaglandins, and production of proinflammatory cytokines, excitatory amino acids, and growth factors establishing pathologic pain.[5,7,8] By inhibiting glial activation and the activation of nuclear factor κB in animal models, glucocorticoids prevent the development of neuropathic pain behavior.[5,7]

Reduced release of neuropeptides from nerve endings, inhibition of signal transmission in nociceptive C fibers and ectopic discharge from traumatized nerves,[9–11] reduced mechanically induced dysesthesia after nerve injury,[12] improved nerve recovery and regeneration,[12–14] and a dose-dependent rapid inhibitory effect on the voltage-dependent calcium currents in dorsal root ganglion neurons[15] are all documented effects of glucocorticoids that may contribute to analgesia.

Rapid antihyperalgesic effects of glucocorticoids have been demonstrated in animals and humans.[2,16,17] Reduction in neural discharge within seconds to a few minutes due to nongenomic steroid effects on membrane receptors has been observed.[18] These rapid nongenomic effects of glucocorticoids are due, at least in part, to decreased glutamate release and increased release of γ-aminobutyric acid and endocannabinoids.[19,20] By decreasing glutamate and increasing γ-aminobutyric acid, glucocorticoids would be expected to rapidly cause a marked reduction in excitability of nerve cells.[19] A theoretic possibility is that both nongenomic and genomic steroid actions are responsible for the analgesic and antihyperalgesic effect, where the nongenomic mechanisms lead to the rapid analgesia and antihyperalgesia (minutes) and the genomic mechanisms give a sustained analgesia and antihyperalgesia (hours to days).

The study by Li *et al.*[1] confirms previous animal and human studies that have found analgesic effects of glucocorticoids on acute postoperative pain, and proposes effects on persistent neuropathic pain after surgical procedures that involve nerve injury. In sharp contrast to the current study by Li *et al.*[1] and other experimental and clinical trials,[2,17,21–24] several studies have demonstrated that glucocorticoid receptors in the spinal cord are up-regulated after constriction nerve injury, and indicate that glucocorticoids can exacerbate neuropathic pain behavior.[25–28] Therefore, at present, results from animal studies on the effect of glucocorticoids after nerve injury are conflicting. The direct relevance of the animal models as predictors of human clinical pain response is difficult to entangle.[29] So far, animal studies on this field need verification in human models before clinical implementation. Regarding glucocorticoid use in humans, there are already convincing evidence for acute analgesic and antihyperalgesic effects of glucocorticoids after surgery and experimental injuries.[2,17,21–24]

Even if human studies are less equivocal than animal studies, the effects on pain after surgery have not been convincing in all clinical studies.[30] Differences in anesthesia methods, surgical technique, use of other analgesics (such as paracetamol or nonsteroidal antiinflammatory drugs in the placebo group), main outcome measures other than pain (usually postoperative nausea and vomiting), and small studies with low power may all be confounding factors in such studies.[22] The dose of glucocorticoid and the extent of the surgical trauma may also influence the analgesic effect. Major surgery may cause such high levels of endogenous cortisol that the benefit of additional exogenous glucocorticoids on pain may be small.[22] But even after major surgery, benefits have been demonstrated, such as reduced inflammatory response, improved pulmonary function, less fatigue, less postoperative nausea and vomiting, appetite stimulation, and more rapid convalescence.[30,31]

Acute postoperative pain is usually considered as inflammatory and nociceptive, but neurogenic mechanisms also contribute, and reversible neuropathic pain may dominate from the late acute phase.[32,33] When postoperative hyperalgesic or allodynic pain persists beyond the usual time of healing, or 3–6 months, it is defined as "chronic postoperative pain" and may persist for months or years.[33,34] This process is probably initiated by peripheral nerve injury and central sensitization occurring at an exaggerated degree causing dysfunctional adaptations of the neurons in the pain-regulating system.[35,36]

Chronic neuropathic pain occurs in 10–50% of patients after surgery[37] and always has components of hyperphenomena and/or hypophenomena indicating nerve damage and central sensitization. Steroids given after oral and orthognathic surgery prevent sensory hypersensitivity.[38,39] Preincisional administration of methylprednisolone attenuated hyperesthesia at 6 weeks and 1 yr after breast augmentation surgery.[40] The same study demonstrated that hyperesthesia 6 weeks after surgery is a risk factor for persisting pain after 1 yr. A recent study in male volunteers demonstrated that methylprednisolone rapidly suppresses central sensitization, shown as reduction of burn-induced secondary hyperalgesia,[17] suggesting a role for glucocorticoids in preventing long-term sensitization.

Sustained postoperative opioid sparing and pain relief continuing for 3 days after one single dose of glucocorticoids (methylprednisolone or dexamethasone) have been reported.[23] This cannot be explained by the duration of the biologic antiinflammatory effect (36 h for methylprednisolone).[30] Reduction in central sensitization reducing postoperative hyperalgesia may contribute to this prolonged analgesic and opioid-sparing effect.

The objection to the use of glucocorticoids perioperatively has been a presumed risk for side effects. However, one single dose of a glucocorticoid (1–2 mg/kg methylprednisolone or 0.2–0.4 mg/kg dexamethasone intravenously) is enough to give a prolonged analgesic and opioid-sparing effect (for 72 h) after surgery.[23] A systematic review of data from more than 1,900 patients concluded that perioperative methylprednisolone up to 30 mg/kg, as a single dose, was not associated with any adverse effects.[41] However, it is important to be aware that glucocorticoids can give a marked but transient elevation in blood glucose.[30]

Sustained analgesic and antihyperalgesic effect, no problems with bleeding or allergy, no renal or respiratory adverse effects, no increase in infection risk, no increase in wound dehiscence, potent antiemetic effects, and a more rapid convalescence are all arguments for a perioperative single dose of a glucocorticoid. However, not all studies investigating glucocorticoids after major surgery have found analgesic effects.[30] And although we believe it is safe to give one dose of a glucocorticoid, what happens when we combine it with nonsteroidal antiinflammatory drugs or coxibs? We suppose that it is safe, but safety data on drug combinations perioperatively are lacking.

In summary, there is evidence that glucocorticoids alleviate acute and continued postoperative pain by suppressing inflammatory mediators, glial activation, reducing neural activity, sympathetic sprouting, and central neuroplastic changes such as central sensitization. Li *et al.*[1] have revealed mechanisms of glucocorticoid action indicating that they may have a role in reducing chronic postoperative neuropathic pain. Although experimental studies on rats are conflicting, there is evidence supporting the perioperative use of glucocorticoids for the relief of acute and sustained postoperative pain. What we now need is properly sized studies investigating long-term effects of perioperative glucocorticoids on human postoperative pain.

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