Efficacy and Safety of Steroid Use for Postoperative Pain Relief. Update and Review of the Medical Literature

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Current Concepts Review

Efficacy and Safety of Steroid Use for Postoperative Pain Relief

Update and Review of the Medical Literature

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- Despite the availability of various analgesic regimens, patient surveys have indicated that moderate-to-severe postoperative pain is still poorly managed.
- The use of corticosteroids for postoperative pain relief, although popular, has yet to gain wider acceptance because of concerns over side effects, in particular adrenal suppression, osteonecrosis, impaired wound-healing, and concerns about efficacy. The medical literature provides evidence that should substantially decrease these concerns with regard to low and short-dose applications.
- The results of randomized trials have shown low, short-dose corticosteroid regimens to be safe and effective for reducing postoperative pain.
- There is strong, grade-A evidence supporting the use of corticosteroids in multimodal analgesia protocols to contribute to the postoperative recovery of the patient by minimizing opioid doses and therefore side effects. However, the optimal mode, dose, and timing of administration remain unclear.

Inadequate postoperative pain relief can delay recovery, necessitate rehospitalization or increase the duration of the hospital stay, increase health-care costs, and reduce patient satisfaction[1-3]. A recent survey investigation of the severity of pain following ambulatory surgery in 5703 patients indicated that 30% (1712) of the patients experienced moderate-to-severe pain postoperatively[4]. Other studies revealed that 77% (104 of 135)[5], 30% (sixty-one of 206)[6], and 57% (1222 of 2144)[7] of patients experienced moderate-to-severe pain following an operation and this pain had been poorly controlled in many cases. Patient surveys in general have indicated that moderate-to-severe postoperative pain is not often managed well despite the various analgesics that are now available[3,8,9].

Fleischli and Adams[10] reviewed the literature on the use of postoperative steroids to reduce pain and inflammation across various medical specialties and concluded that the evidence supported the administration of steroids following a variety of surgical procedures[11-25]. Callery[26] acknowledged the beneficial effects of steroids with regard to decreasing nausea, vomiting, and pain following limited surgical trauma such as that caused by tonsillectomies, dental procedures, and laparoscopic cholecystectomies. More recently, Gilron[27] concluded that the current evidence suggests that systemic corticosteroids are efficacious in the treatment of postoperative pain, nausea, and vomiting but more research is needed to clearly delineate their role. Furthermore, Holte and Kehlet[28] investigated the effects of glucocorticoids on the strong inflammatory response typically seen following cardiopulmonary and major abdominal surgery and found that a single dose of glucocorticoid inhibits the synthesis and release of proinflammatory and anti-inflammatory mediators. Steroid administration to address postoperative pain is still evolving, and the literature supports its use in various surgical subspecialties. The purpose of this article is to update and review the literature on postoperative analgesics and the efficacy and safety of steroid use in the management of postoperative pain. The review of the published medical literature includes assignment of a level of evidence to each of the papers to enable the strength of the evidence to be judged[29].

Steroid Characteristics

Glucocorticoids, also known as corticosteroids, have the most powerful anti-inflammatory characteristics of all steroids. Corticosteroids are a subgroup of compounds known as adrenocorticoids that are naturally secreted from the adrenal gland. The primary corticosteroid is hydrocortisone, which is the standard against which the pharmacological properties of various synthetic corticosteroids are judged. Many synthetic agents that are more potent, have longer durations of action, have greater anti-inflammatory activity, and generate fewer unwanted mineralo-

TABLE I Characteristics of Corticosteroid Preparations

Drug	Anti-Inflammatory Potency*	Sodium-Retaining Potency*	Biologic Half-Life *(hr)*	Equivalent Dose *(mg)*	Mineralocorticoid Potency*	Glucocorticoid Potency*
Short-acting						
Hydrocortisone	1	1	8-12	20	1	1
Cortisone	0.8	0.8	8-12	25	0.8	0.8
Intermediate						
Prednisolone	4	0.8	18-36	5	0.8	4
Prednisone	4	0.8	18-36	5	0.8	3.5-5
Methylprednisolone	5	0.5	18-36	4	0.5	5-7.5
Triamcinolone	5	0	18-36	4	0	5
Long-acting						
Dexamethasone	25	0	36-54	0.75	0	25-80
Betamethasone	25	0	36-54	0.75	0	25-30

*The relative potency, with hydrocortisone used as the standard with a value of 1.

corticoid side effects than hydrocortisone have been developed. Mineralocorticoids are adrenal cortical steroid hormones that have a greater effect on water and electrolyte balance than do corticosteroids. The main endogenous hormone is aldosterone. Different steroids vary with respect to their duration of action and relative corticosteroid and mineralocorticoid activity. Corticosteroids are divided into short, intermediate, and long-acting groups (Table I). Short and long-acting preparations cause less inhibition of the hypothalamic-pituitary-adrenal axis[30]. Many of the unwanted side effects are related to the mineralocorticoid properties[31].

Nearly all routes of administration can be used for corticosteroids. Corticosteroids administered through the oral route are rapidly and virtually totally absorbed. The water-soluble ester forms of the drug can be delivered intravenously or intramuscularly to achieve high concentrations systemically, whereas the acetate forms are relatively insoluble in water and can be administered only intramuscularly. The intramuscular route provides slow absorption but a prolonged duration of action. Factors that influence both the therapeutic and the adverse effects of corticosteroids include the pharmacokinetic properties of the glucocorticoid, the daily dosage and the timing of doses during the day, individual differences in steroid metabolism, and the duration of treatment[32].

Pathophysiology of Postoperative Pain

Surgery causes mechanical tissue damage, and pain is a direct response to this event. The cause is clear, and the pain can be regarded as a normal response to tissue injury. It is termed *nociceptive pain,* and it decreases as the tissue damage resolves (Fig. 1). The surgical incision is the initial insult to tissues, causing mechanical distortion of sensitive nerve terminals and activation of receptors that generate the first pain transmission to higher centers to trigger pain appreciation. Acute postoperative pain can be considered a complex relationship among three components: afferent nociceptive stimulation, interpretation and modulation of these signals by higher centers (involving memory and previous experiences), and an affective component (involving fear, anxiety, and depression). As such, the degree of postoperative pain experienced by patients can vary enormously. Understanding the pathophysiology of pain and the concepts of nociceptive pain therapy is important so that surgeons can provide adequate pain control for their patients.

Nociceptive Stimulation, Dorsal Horn Modulation, and Descending Inhibition

Nociceptive transmission takes place in both the large, fast myelinated A-delta fibers connected to mechanoreceptors and the nonmyelinated, more slowly conducting C-fibers connected to nociceptors (polymodal nociceptors). The release of a number of algesic substances affects the C afferent terminal by reducing the threshold for further stimulation for the generation of pain impulses[32-34]—that is, peripheral sensitization, which is recognized as initiating change in the pain pathway that increases the pain experienced by the individual. Once activated, nociceptors transmit action potentials along afferent nerve fibers to the spinal cord. Inhibition at the peripheral level can be achieved with nonsteroidal anti-inflammatory drugs, steroids, peripherally applied opioids, serotonin (5-HT) antagonists, and local anesthetics. Neural block of A-alpha and C-nociceptive fibers occurs with administration of peripheral, extradural, or spinal local anesthetics.

The afferent nociceptive pain fibers synapse in the dorsal horn of the spinal cord with other non-nociceptive neurons. Large non-nociceptive A-beta fibers originating from the periphery or neurons descending from the spinal cord may inhibit pain-transmission neurons or interconnecting neurons. Pain transmission is regulated by balancing the firing of the C and A-delta fibers with the firing of large non-nociceptive A-beta fibers. In short, C-fiber activity opens the gate for pain transmission and A-beta fibers close it[35]. An understanding of this interplay of neuronal activity has permitted greater comprehension of nonpharmacological treatment modalities such as massage, local irritants, heat, cold, acupuncture, and transcuta-

neous electrical nerve stimulation in pain management (Fig. 1)[36]. The synapse between the C-afferent neurons and neurons that respond to a wide range of inputs, so-called wide-dynamic-range neurons, in the dorsal horn allows modulation so that the activity is either increased or decreased. The wide-dynamic-range neuron may respond with bursts of activity that amplify the pain signal in what is known as central sensitization or the wind-up phenomenon[32,36]. This is caused by N-methyl-D-aspartate receptor activation, and antagonists to these receptors have been shown to inhibit dorsal horn wind-up. This is the site of action where ketamine, serotonin, tricyclic antidepressants, and opioids block central sensitization.

Following modulation, the pain impulses travel from the dorsal horn along a complex array of ascending spinal cord pathways, of which the spinothalamic tract is the most important for pain transmission, and project to a number of nuclei in the thalamus. From the thalamus, the terminal sites of pain appreciation are the somatosensory cortex (sensory aspect of pain) and the limbic system (affective component of pain). The cortex is considered to be the ultimate site of conscious awareness of sensory stimuli. Higher centers are the likely sites of influence by behavioral-cognitive therapies, systemic opioids, and alpha 2-agonists (Fig. 1)[32].

Descending inhibitory pathways originate in the sensory

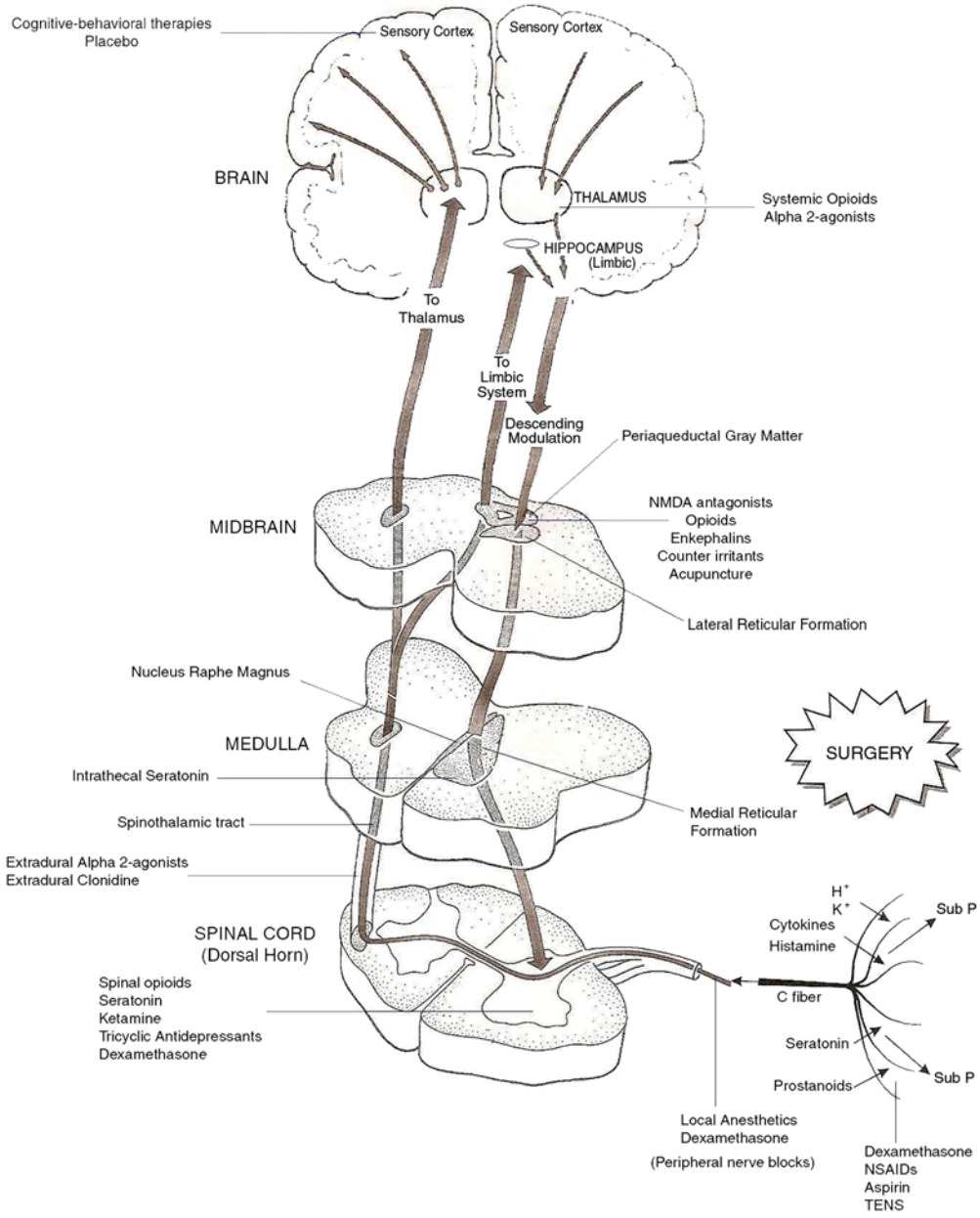

Fig. 1

Pain transmission, modulation, and sites of action. NMDA = N-methyl-D-aspartate.

cortex of the brain and end in the dorsal horn of the spinal cord. Pain-suppressing impulses originate in the periaqueductal grey matter in the midbrain and the rostral ventromedial medulla and reduce pain sensation by blocking the passage of nociceptive impulses in the dorsal horn. Opioids, acting at a spinal or supraspinal level; alpha 2-agonists; and N-methyl-D-aspartate antagonists activate descending inhibitory pathways (Fig. 1)[32].

Analgesic Drugs in Postoperative Pain Management

Nonopioid Analgesics

Nonsteroidal anti-inflammatory drugs are considered the drug of choice for mild-to-moderate postoperative pain after many small and ambulatory procedures when there are no contraindications to their use. Nonsteroidal anti-inflammatory drugs have both analgesic and anti-inflammatory properties. They decrease the opioid requirement and enhance the quality of analgesia produced by opioid medications[37]. However, it has been shown that, when used alone, they are not powerful enough to manage severe pain in most patients[38]. Indomethacin, tenoxicam, ketorolac, diclofenac, and ibuprofen have been found to be useful analgesic drugs after surgery. Ibuprofen is the drug of choice if the oral route is available because it is clinically effective and inexpensive and it has a lower side-effects profile compared with the other nonsteroidal anti-inflammatory drugs[39]. Nonsteroidal anti-inflammatory drugs may be given orally, rectally, or by injection. The new selective cyclooxygenase-2 inhibitors, which have a selective action against COX-2, theoretically produce anti-inflammatory effects without the gastric and renal side effects. These claims of greater safety have been hard to sustain in the clinical setting[40], although the rates of gastric ulceration associated with use of celecoxib and rofecoxib were substantially lower than the rates associated with more traditional nonsteroidal anti-inflammatory drugs in recent studies[41,42].

Contraindications to the use of nonsteroidal anti-inflammatory drugs should be respected because adverse effects are potentially serious[43] and the incidence and severity are greater in the elderly. The most important adverse effects include gastrointestinal ulceration, renal dysfunction, inhibition of platelet function, and induction of asthma. Aspirin, although the most commonly used analgesic throughout the world for the treatment of mild-to-moderate pain, is not suitable for postoperative purposes because of substantial irreversible antiplatelet effects. Paracetamol has analgesic and antipyretic actions but few anti-inflammatory traits. It is effective for mild-to-moderate pain and can be used concomitantly with opioids for more severe pain. Unwanted side effects are few and uncommon, although allergic skin reactions sometimes occur. However, regular intake of large doses over a prolonged period may increase the risk of kidney damage[44]. Paracetamol is available in oral and rectal forms. Propacetamol is a precursor drug recently intro-

TABLE II Potential Side Effects Associated with Corticosteroid Therapy*

Dermatologic and Soft Tissue	**Renal**
Skin thinning and purpura	Hypokalemia
Cushingoid appearance	Fluid volume shifts
Alopecia	**Genitourinary and reproductive**
Acne	Amenorrhea/infertility
Hirsutism	Intrauterine growth retardation
Striae	**Bone**
Hypertrichosis	Osteoporosis
Eye	Avascular necrosis
Posterior subcapsular cataract	**Muscle**
Elevated intraocular pressure/glaucoma	Myopathy
Exophthalmos	**Neuropsychiatric**
Cardiovascular	Euphoria
Hypertension	Dysphoria/depression
Perturbations of serum lipoproteins	Insomnia/akathisia
Premature atherosclerotic disease	Psychosis
Arrhythmias with pulse infusions	Pseudo tumor cerebri
Gastrointestinal	**Endocrine**
Gastritis	Diabetes mellitus
Peptic ulcer disease	Hypothalamic-pituitary–adrenal insufficiency
Pancreatitis	**Infectious disease**
Steatohepatitis	Heightened risk of typical infections
Visceral perforation	Opportunistic infections
	Herpes zoster

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duced in Europe; it is delivered intravenously and is converted to paracetamol. Propacetamol has been proven to be even more effective than paracetamol for postoperative analgesia[45,46].

Opioid Analgesics

Codeine is a weak opioid analgesic derived from morphine, although it is markedly less active than its parent compound. Codeine must be metabolized to morphine in order to exert its analgesic effects. However, approximately 5% to 10% of the white population is unable to convert codeine to morphine because of a deficiency in the CYP2D6 enzyme[47]. Codeine is effective against mild-to-moderate pain and can be combined with paracetamol and nonsteroidal anti-inflammatory drugs. Dextropropoxyphene is also considered a weak opioid; it is structurally similar to methadone but is a relatively poor analgesic in comparison. Although previously thought to be associated with a low risk of drug dependence and to have a substantial margin of safety in the event of overdose, experience has shown neither assumption to be true[48]. It is combined and marketed with paracetamol and offers few if any advantages over codeine. Tramadol has proven to be a weak opioid with analgesic potency similar to that of pethidine (as described below) but without the sedation, respiratory depression, gastrointestinal stasis, or abuse potential. It appears to be well tolerated with few side effects other than nausea and dizziness, and it is available for oral, intramuscular, and intravenous administration.

The strong opioid analgesics (narcotics) should generally be reserved for severe pain arising from deep structures. Morphine is the so-called gold standard against which other opioids are compared. Major side effects include nausea, vomiting, constipation, and respiratory depression. Tolerance may occur with repeated dosage but is unlikely with use in the acute setting. Pethidine is a synthetic opioid with a short half-life requiring hourly administration. Accumulation of its toxic metabolite, norpethidine, following repeated dosing and in patients with renal impairment is a concern, so the use of oral pethidine is not recommended.

Methadone differs from the other agents in that it is well absorbed after it is taken by mouth and it is slowly metabolized in the liver, which makes it more suitable for the treatment of chronic pain rather than acute postoperative pain. Fentanyl is used predominantly for intraoperative analgesia because of its short duration of action. Its side effects are similar to those of morphine, and it has been used intrathecally or epidurally. Buprenorphine can be delivered by the sublingual route, so it is rapidly absorbed, but it is associated with a high incidence of nausea, vomiting, and sedation. Nalbuphine and butorphanol have been used to provide postoperative analgesia with intermittent, continuous, and patient-controlled analgesia techniques. These drugs exhibit a ceiling effect for analgesic activity, which has limited their popularity.

Nonpharmacological Approaches to Pain Relief

Some nonpharmacological approaches to pain relief are available and have often been used adjunctively with conventional pharmacological treatments. Cognitive-behavioral therapies are nonpharmacological interventions that change the way that people with pain perceive and react to that pain. These therapies focus on the overt behavior and thought processes of patients, including how the patient interacts with medical and nursing staff and family members. Pain catastrophizing has been defined as an exaggerated negative mental set brought to bear during an actual or anticipated painful experience and has been identified as one of the strongest psychological predictors of pain[49,50]. Identifying patients who are prone to catastrophizing before an operation may allow the surgeon to intervene with preemptive psychological or pharmacological modalities. There is a high level of evidence supporting the use of cognitive-behavioral therapies such as relaxation training, provision of procedural information, cognitive coping methods, and behavioral instruction in postoperative pain management. Johnston and Vogele[51] conducted a meta-analysis and found that the aforementioned psychological interventions reduce the analgesic requirement, improve pain scores, and improve recovery postoperatively.

Transcutaneous electrical nerve stimulation is widely used to control acute and chronic pain, but its clinical efficacy appears to be poor. Its suggested action is stimulation of non-pain afferent fibers (A-alpha), which in turn activate modulation pathways at the spinal cord level. In a systematic review of studies of transcutaneous electrical nerve stimulation for postoperative pain management (level I), Carroll et al.[52] found no benefit compared with a placebo. Hargreaves and Lander reported no significant difference between real and sham transcutaneous electrical nerve stimulation procedures: both produced the same degree of analgesia and subjective reports of pain relief, suggesting a placebo effect[53]. Furthermore, an experimental study by Reeves et al.[54] (level I) demonstrated no evidence that transcutaneous electrical nerve stimulation affected either the function of the sympathetic nervous system or the perception of acute experimental pain.

Potential Side Effects Following Corticosteroid Use

Corticosteroids have adverse effects on many organ systems and thus numerous potential side effects[55-57] (Table II). The clinical effects of chronic, excessive use of corticosteroids on connective tissue include impaired wound-healing, skin-thinning and purpura, and cushingoid features (truncal obesity, buffalo hump, moonface, and weight gain). Corticosteroids also have many effects on innate and acquired immunity that predispose to infection[58]. They also dampen the febrile responses to bacterial infections, making these infections difficult to detect. Infections with atypical or opportunistic organisms were seen more than forty times more often in patients who were given glucocorticoids than in those who were not[59]. Cataract formation is another side effect, which some believe is dose and time-dependent[60], whereas others believe that there is no minimal safe dose with respect to this complication[61]. Corticosteroids can also increase intraocular pressure, causing glaucoma[62]. Therapeutic use of supraphysiologic doses of glucocorticoids may also

TABLE III Recommendations for Postoperative Pain Management in Bone and Joint Surgery

Intervention	Grade of Recommendation*	Comment/Application
Nonsteroidal anti-inflammatory drugs		
Oral (alone)	A (against)	Mild pain only
Oral (with opioid)	A	Moderate/severe pain
Paracetamol		
Oral (alone)	A (against)	Mild pain only
Oral (with opioid)	A	Moderate/severe pain
Opioid		
Oral	A	
Intramuscular	A	Painful; unreliable absorption
Subcutaneous (infusion device)	A	
Intravenous	A	Choice in major surgery
Patient-controlled anesthesia (systemic)	A	
Epidural/intrathecal	A	
Local anesthetics		
Epidural/intrathecal	A	
Peripheral nerve block	A	
Corticosteroids		
Subcutaneous (with local anesthesia)	A	
Intravenous (with patient-controlled anesthesia)	A	
Intra-articular (with local anesthesia)	A	
Nonpharmacological methods		
Transcutaneous electrical nerve stimulation	A (against)	
Psychological therapies	A	
Acupuncture	I	

*A = good evidence (Level-I studies with consistent findings) for or against recommending intervention, B = fair evidence (Level-II or III studies with consistent findings) for or against recommending intervention, C = poor-quality evidence (Level-IV or V studies with consistent findings) for or against recommending intervention, and I = insufficient evidence or conflicting evidence not allowing a recommendation for or against intervention.

be associated with increased rates of myocardial infarction, stroke, heart failure, and mortality from all causes[63,64]. Corticosteroids may increase the risk of peripheral atherosclerotic vascular disease as well[65].

Corticosteroids independently increase the risk for a number of adverse gastrointestinal events, such as gastritis, ulcer formation, and gastrointestinal bleeding. The combination of corticosteroids and nonsteroidal anti-inflammatory drugs results in a synergistic increase in the incidence of gastrointestinal events[66,67]. Corticosteroids may mask the symptoms of serious gastrointestinal disease. Corticosteroids also have a number of effects on renal function and systemic hemodynamics, commonly promoting fluid retention, a particular concern to patients with underlying heart or kidney disease. Corticosteroid therapy can raise the blood pressure both in people with hypertension and in those with normal blood pressure[68]. High doses of corticosteroids can cause menstrual irregularities in women and can lower fertility in both men and women[69,70]. High serum concentrations of corticosteroids have numerous effects on bone and mineral metabolism, creating fractures. Although low doses are safer than high doses, there is still controversy about whether there is any safe dose of corticosteroid[71-73].

High-dose corticosteroid therapy is an important risk factor for osteonecrosis, but the disease does not develop in all patients with this risk factor. Many theories have been proposed to decipher the mechanism behind the development of osteonecrosis, but none have been proven[74]. Recent research by Asano et al.[75] identified specific genotypes related to the metabolism of corticosteroids that may play an important role in identifying patients who are at risk for the disease.

Myopathy is an infrequent complication of corticosteroid therapy. Growth impairment is commonly seen in children receiving corticosteroids. Patients with a family history of depression or alcoholism are at increased risk for affective diseases when they are given glucocorticoids[76]. Symptoms such as akathisia, insomnia, and depression can be seen even in patients taking low doses. Psychosis can occur, but almost exclusively in association with doses of prednisone of >20 mg/day given for a prolonged period[77]. Corticosteroids have a variety of actions that lead to hyperglycemia. Patients with diabetes mellitus or glucose intolerance exhibit higher blood glucose levels while taking gluco-

corticoids, which increases difficulty with glycemic control. Corticosteroid-induced diabetes lessens in severity with a reduction in the dose of corticosteroids and it may fully resolve when the medication is stopped.

Orthopaedic and Podiatric Surgery

Intra-articular injections of corticosteroids for the treatment of inflammatory joint pain and swelling following arthroscopic knee surgery have received little attention in the literature. The mainstays for pain relief after total hip arthroplasty and total knee arthroplasty have been the opioids, but although these medications are excellent analgesics, they have problems that limit their effectiveness. Alternative analgesics have been considered too mild for the pain caused by total hip arthroplasty and total knee arthroplasty. However, some studies of the use of corticosteroids in orthopaedic surgery are available, and we will review those studies as well as provide a rating of the level of evidence in parentheses for each article[29].

Highgenboten et al.[19] (level I) reported that oral use of corticosteroids had no significant effects on analgesic intake, pain as measured with a visual analogue scale, or functional outcome following arthroscopic knee surgery. In a study of sixty-two patients treated with repair of the anterior cruciate ligament (level III), Vargas and Ross[78] examined the effects of oral and intravenous dexamethasone on analgesic use, duration of hospitalization, and the day on which the patient first walked. During hospitalization, the treatment group showed a 50% reduction in the use of analgesics (mean, 14.19 doses) compared with the control group (mean, 21.29 doses). Similarly, the treatment group had a shorter hospital stay (mean, 3.61 compared with 5.74 days) and walked sooner (at a mean of 1.93 days compared with a mean of 2.67 days) than the control group. The surgery performed in the study by Vargas and Ross would have resulted in much greater swelling, pain, and surgical trauma compared with that done in the study by Highgenboten et al. The difference in the findings between the two studies may be due to the fact that corticosteroids do not produce changes in the pain parameters when there is not enough pain, edema, and trauma. Additionally, different steroids and different administration times were used, making it difficult to compare the findings of the two studies. However, Wang et al.[79] (level I) found that patients who had been treated with 10 mg of triamcinolone intra-articularly at the end of arthroscopic knee surgery had lower pain scores than a control group from six hours ($p < 0.05$) to twenty-four hours ($p < 0.001$) postoperatively. Furthermore, the proportion of patients requesting rescue analgesia was significantly ($p < 0.001$) greater in the control group (sixteen of thirty) than in the group that had received corticosteroids (zero of thirty). This observation supports the findings of Vargas and Ross, but again methodological inconsistencies make comparison of the studies difficult.

Kizilkaya et al.[80] (level I) reported that administration of sufentanil with methylprednisolone in the knee joint after arthroscopic meniscectomy reduced pain ($p < 0.05$) and the use of analgesics ($p < 0.05$) significantly compared with administration of sufentanil alone and reduced it even more compared with administration of saline solution ($p < 0.05$). A similar study conducted by Rasmussen et al.[81] (level I) showed that the addition of methylprednisolone to the analgesia regimen further reduced pain, joint swelling, the duration of immobilization, and the need for rescue analgesics ($p < 0.05$). However, Lee et al.[82] (level I) reported that use of dexamethasone had no influence on pain intensity and did not enhance the efficacy of patient-controlled analgesia with morphine following major orthopaedic surgery. However, the single low dose of dexamethasone that was administered in that study may not have been appropriate to render pain relief following major orthopaedic surgery, especially when compared with the higher doses and longer dosing regimen used in the study by Highgenboten et al.[19].

Subcutaneous injection of a steroid has been and continues to be used by many foot and ankle surgeons to reduce pain and inflammation after foot surgery[83-85]. There are few studies of the use of corticosteroids for postoperative pain relief in the podiatric surgery literature, despite its popularity. Curda[14] (level I) showed that use of dexamethasone reduced pain more effectively at twenty-four hours postoperatively ($p < 0.0001$) and four to seven days postoperatively ($p = 0.0004$) compared with use of bupivacaine alone. In a similar study (level II), Tiberia et al.[86] found that 65% (forty-four) of sixty-eight patients did not require any form of analgesia during the first four hours after surgery, 44% (thirty) did not require it during the first eight hours, 28% (nineteen) did not require it during the first twelve hours, and 16% (eleven) required no form of analgesia during their entire hospital stay. No statistical analysis was conducted in that study. Bryant et al.[87] conducted a retrospective analysis (level III) supported by statistical data that revealed a marked reduction in the need for narcotics and oral analgesics in a group in which dexamethasone had been injected compared with a group that had not been treated with dexamethasone. Aasboe et al.[88] (level I) evaluated the effects of a single dose of glucocorticoids on the incidence and severity of pain, nausea, and vomiting after ambulatory surgery for hallux valgus. Patients treated with steroids experienced significantly less postoperative pain in the first twenty-four hours after surgery ($p < 0.001$), and more of those patients expressed general overall satisfaction at that time-point ($p < 0.001$). The limitation of that study was the small sample size. In contrast to the findings of Aasboe et al., Miller and Wertheimer[25] (level II) did not find any improvements after the use of dexamethasone; however, no statistical evidence was provided to strengthen their study results.

Neurosurgery

Many neurosurgeons have applied long-acting local anesthetic agents with steroids intraoperatively to decrease postoperative pain following lumbar discectomy performed to reduce traumatic nerve-root inflammation. The efficacy of this multimodal therapy in conjunction with lumbar discectomy has been a popular area of investigation, particularly over the last few years.

King's[89] study (level I) confirmed that intravenous dexamethasone reduces postoperative pain following lumbar dis-

cectomy, as demonstrated by a significant reduction ($p \leq 0.01$) in the quantity of narcotics used during the first seventy-two hours after surgery. Watters et al.[90] (level I) found that oral and intravenous administration of dexamethasone significantly reduced pain ($p < 0.025$), narcotic consumption ($p < 0.005$), and duration of the hospital stay ($p < 0.05$) postoperatively. Similarly, Foulkes and Robinson[91] (level I) reported that, compared with a control group, patients treated with intraoperative irrigation with dexamethasone had a significant reduction in the duration of hospitalization ($p < 0.001$) and a highly significant reduction in narcotic consumption ($p < 0.001$).

Glasser et al.[18] (level I) showed that patients in whom the wound had been infiltrated with methylprednisolone and bupivacaine had a significant reduction ($p = 0.0004$) in the hospital stay (mean, 1.4 days) compared with a control group (mean, 4.0 days) and also required fewer doses of injectable narcotic analgesia ($p < 0.01$) compared with the control group. Langmayr et al.[20] (level I) found that a group in which betamethasone had been used intrathecally before wound closure had a significantly more rapid reduction of pain compared with a control group ($p < 0.001$), in which the pain declined gradually. However, there was no difference in the consumption of nonsteroidal anti-inflammatory drugs by the two groups. Mirzai et al.[92] (level I) more recently found that pain scores were lower in a group treated with bupivacaine and a methylprednisolone-soaked fat graft than they were in a group without such treatment, but the findings were not significant. However, the use of the bupivacaine and corticosteroids maintained effective postoperative analgesia and decreased opioid use, without complications, compared with that in the control group ($p < 0.05$). Lundin et al.[93] (level I) reported that, compared with a control group, a group treated with methylprednisolone had a shorter hospital stay ($p = 0.01$), returned to full-time work sooner ($p = 0.003$), and had a greater reduction in pain ($p = 0.02$). Similarly, Karst et al.[94] (level I) found that patients who had been treated with dexamethasone intraoperatively required less postoperative patient-controlled anesthesia ($p = 0.001$) and had lower pain scores and von Frey thresholds ($p = 0.003$) than a group without such treatment. Glasser et al., Mirzai et al., and Lundin et al. all used similar techniques, albeit with different dosing regimens and different steroids.

In contrast with all of the aforementioned findings, Lavyne and Bilsky[95] (level I) reported that a group that had received an epidural injection of methylprednisolone after microdiscectomy did not have a greater reduction in pain, as measured on the basis of analgesic requirements, or improved functional recovery as compared with a control group. This result may be attributed to the lack of steroids in and around the surgical site and the lateness of the administration compared with that in the other studies.

Corticosteroids: Mechanism of Action

Local anesthetics are widely administered in the ambulatory surgical setting, with use of techniques such as local injection, field block, regional nerve block, or neuraxial block. Introduction of a steroid with the local anesthetic has a clear benefit in terms of prolonging the duration of the analgesia in a safe and effective manner[14,16,18,24,87,91,96]. A single low dose of dexamethasone mixed with bupivacaine and administered as a preemptive subcutaneous injection is customarily used in podiatric surgery[14,86,87]. The biologic half-life of dexamethasone is thirty-six to fifty-four hours, and its effects are most apparent in the first twenty-four to forty-eight hours. Dexamethasone is preferred both in foot and ankle surgery and in spinal surgery, perhaps because of its decreased mineralocorticoid activity, its potent anti-inflammatory activity, and its lower sodium-retention effects. Dexamethasone also has an appropriate duration of action that maintains therapeutic levels throughout the postoperative period in which inflammation is greatest—namely, in the first phase of wound-healing at three to four days. The above-described mode of administration has the added benefit of delivering higher local concentrations of steroid while minimizing systemic exposure.

The prevention of peripheral and central sensitization by preemptive analgesia must include a way of modulating the prolonged neuronal input into the spinal cord in the postoperative period that is produced by the inflammatory process at the site of tissue damage[26,97,98]. Inflammatory, metabolic, hormonal, and immune responses to surgery are activated immediately after the surgical incision, so preoperative administration of steroids may be important to obtain the full postoperative benefit[99-101]. Dexamethasone and other steroids may prove beneficial in reducing these responses by virtue of their anti-inflammatory and immunosuppressive effects. Also, a direct inhibitory effect of locally administered steroids on signal transmission in nociceptive C-fibers has been demonstrated[28]. One subcutaneous injection of dexamethasone with bupivacaine appears to address peripheral sensitization and inflammatory surgical injury adequately. An injection before surgical trauma is in keeping with the concept of preemptive analgesia so that nociceptive information is not being processed, theoretically reducing the amount of pain postoperatively[102,103]. The pain relief following the surgery is then maintained with balanced or multimodal analgesia, with a combination of nonsteroidal anti-inflammatory drugs and weak opioids. This approach appears to improve the effectiveness of pain relief after surgery[104-106]. There may also be an associated reduction in the dose of each analgesic drug, thus lowering the overall prevalence of side effects[78,79,93]. Another potential benefit of steroid use is the apparent postoperative antiemetic and antinausea effects reported in many studies[88,99,107-110].

In foot and ankle surgery, for example, a single low (4 to 8-mg/mL) dose of dexamethasone is often administered, with a local anesthetic agent subcutaneously or as a peripheral nerve block, to further minimize the risk of systemic side effects. An understanding of the neuroanatomy of the foot is required to achieve successful anesthesia and analgesia intraoperatively and postoperatively. The subcutaneous route of administration has the added advantage of allowing acetate drug forms to be used, so the duration of action is longer.

Safety of Low-Dose Short-Course Corticosteroid Therapy

Treating postoperative pain with steroids is not the mainstream approach, probably because of concerns about complications[111]. Corticosteroid toxicity is one of the most common causes of iatrogenic illness associated with chronic inflammatory disease. A true cause-and-effect relationship between corticosteroid therapy and some of its apparent side effects has not been clearly delineated. Confounding factors may bias perceived associations. Many studies of steroid side effects have been conducted in the field of rheumatology because of the potent inflammatory component of disease states seen by practitioners of this specialty and their need to control the inflammation. When reviewing studies of corticosteroid-associated side effects, particularly in the context of rheumatology, one must appreciate the reason for the initial steroid use, since patients who use these drugs are generally sicker than those with similar conditions who are not treated with corticosteroids. In addition, accompanying illness and use of other medications may be directly associated with side effects.

It has been demonstrated that side effects from corticosteroid use are proportional to the duration and intensity of therapy and that long-term, low-dose corticosteroid use is an independent predictor of numerous serious side effects[112-114]. The literature clearly reflects the safety of short-term use of corticosteroids for acute postoperative analgesia in relatively healthy individuals.

Long-term suppression of the hypothalamic-pituitary-adrenal axis with a single high dose of steroids has caused major concern, but many investigators do not believe that it is a problem[115-122]. High-dose treatment, even a single 8-mg dose of dexamethasone in conjunction with oral surgery, has been seen to partially suppress the hypothalamic-pituitary-adrenal axis for up to a week[121,123]. However, this suppression is a clinically benign and reversible condition. Friedman et al.[124] (level II) explored the need for supplemental stress steroids in the perioperative period and concluded, on the basis of biochemical tests of the function of the hypothalamic-pituitary axis and clinical findings, that biochemical tests are too sensitive and that adrenocortical insufficiency appears to be rare. Although this was not a randomized or controlled trial and the sample was small, the findings were consistent with those in a number of previous studies[125-128].

Side effects of the use of steroids are related to the high mineralocorticoid activity and/or long-term dosing[31,129-131]. In a systematic review of data on 1900 patients in whom perioperative methylprednisolone had been used in major surgery for trauma or spinal cord injuries, Sauerland et al.[132] found no adverse side effects. Prophylactic intravenous administration of dexamethasone was deemed a safe and effective choice for preventing postoperative nausea and vomiting in a study of 168 children undergoing surgery for strabismus[133]. Specifically, there was no significant increase in blood glucose levels, and none of the patients had a wound infection or delayed wound-healing. In a quantitative systematic review (level III) of the use of dexamethasone for prevention of postoperative nausea and vomiting, Henzi et al.[109] specifically looked for and found no evidence of adverse effects. Furthermore, the administration of dexamethasone after tonsillectomy appears to be safe; in particular, postoperative bleeding rates were found not to be affected in the groups that had received the steroid[134].

Some surgeons have concerns about steroids masking the clinical signs of infection. However, such concerns should not apply to a single low dose of steroids if one considers the biologic half-life of dexamethasone (thirty-six to fifty-eight hours). It is most likely that an infection would be masked within that window of greatest activity, but following orthopaedic and podiatric surgery, for example, it is customary for a postoperative wound to be redressed at one week, at which time the corticosteroid would have been totally eliminated from the body. Therefore, if an infection was present at that time, the clinical signs would be evident on examination of a non-immunocompromised patient. Studies of patients with severe asthma[135] or ulcerative colitis[136] who had undergone surgical procedures failed to reveal an increased wound infection rate in association with the use of perioperative steroids. Furthermore, no detrimental side effects in terms of wound-healing were demonstrated in random, controlled trials of patients treated with major abdominal surgery[137,138], dental surgery[139], or laparoscopic cholecystectomy[140]; a meta-analysis of the use of dexamethasone to prevent postoperative nausea and vomiting[109]; studies of patients undergoing orthopaedic surgery[82,141]; or a large trial involving trauma patients, patients undergoing major surgery, and patients with spinal cord injuries[132].

In conclusion, steroids, with or without local anesthetic agents, have been administered by surgeons across various medical specialties and with use of different methods (Table III). The ideal dose and mode of administration are yet to be determined, but there is overwhelming evidence that corticosteroids increase the efficacy of pain reduction following surgery in a manner that does not compromise patient safety. This approach is simple and inexpensive. However, there is still a need for large, randomized, double-blind, placebo-controlled studies to validate the use of dexamethasone with bupivacaine or similar combinations as protocols of choice for preemptive analgesia in orthopaedic surgery.

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