Review

Corticosteroids and wound healing: clinical considerations in the perioperative period

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KEYWORDS: Corticosteroids; Wound healing; Perioperative

Abstract

BACKGROUND: Determining whether systemic corticosteroids impair wound healing is a clinically relevant topic that has important management implications.

METHODS: We reviewed literature on the effects of corticosteroids on wound healing from animal and human studies searching MEDLINE from 1949 to 2011.

RESULTS: Some animal studies show a 30% reduction in wound tensile strength with perioperative corticosteroids at 15 to 40 mg/kg/day. The preponderance of human literature found that high-dose corticosteroid administration for <10 days has no clinically important effect on wound healing. In patients taking chronic corticosteroids for at least 30 days before surgery, their rates of wound complications may be increased 2 to 5 times compared with those not taking corticosteroids. Complication rates may vary depending on dose and duration of steroid use, comorbidities, and types of surgery.

CONCLUSIONS: Acute, high-dose systemic corticosteroid use likely has no clinically significant effect on wound healing, whereas chronic systemic steroids may impair wound healing in susceptible individuals.

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The effects of corticosteroids on wound healing have been a topic of great interest among surgeons, internists, and dermatologists. Within the past century, pivotal discoveries in the mechanisms of wound healing have enhanced our understanding of the molecular interactions between corticosteroids and cutaneous wounds.1-11 These basic science discoveries, coupled with findings from clinical studies, have highlighted several important considerations regarding perioperative corticosteroid administration, namely, dosing, chronicity, and timing relative to surgery.

In 1949, Hench et al12 revolutionized the treatment of rheumatologic patients when they reported dramatic improvement of rheumatoid arthritis symptoms in patients treated with 50 to 100 mg of 17-hydroxy-11-dehydrocortisosterone daily. The following year, they were awarded the Nobel Prize in Medicine for this “medical miracle.” Since then, systemic corticosteroids have been used to treat various inflammatory conditions, including rheumatoid arthritis, temporal arteritis, gout, and inflammatory bowel disease, which may require surgical management.

Importantly, the initial report from Hench et al12 did not describe wound healing concerns, but subsequent clinical
reports noted potential adverse effects of corticosteroids on wound healing. Later studies in animal models also showed corticosteroid-induced wound healing impairment at high doses. Thus, when patients on systemic corticosteroids require surgical procedures, concerns may arise regarding postoperative wound complications.

This article reviews the three aspects of the effects of corticosteroids on wound healing. First, the mechanisms of normal wound healing will be summarized, followed by an overview of the molecular interactions between corticosteroids and the wound healing process in the context of a cutaneous wound. Second, data regarding the effects of corticosteroids on wound healing in animal models and humans will be presented. Finally, dosing, chronicity, and timing of corticosteroid administration relative to surgery will be discussed.

Corticosteroid structure and function

Corticosteroids are lipophilic molecules derived from the endogenous hormone cortisol that diffuse into cells, then bind to and activate glucocorticoid receptors (GRs). Activated GRs dimerize and diffuse into the nucleus, where they drive or inhibit gene transcription by binding to glucocorticoid response elements present in the promoter regions of target genes. Structural alterations of the cortisol backbone result in corticosteroids with varying tissue distribution, rate of hepatic metabolism, and affinity for the GR.

Molecular mechanisms of corticosteroids and their effects on wound healing

Corticosteroids have been shown to affect all major steps of the wound healing process, which is somewhat arbitrarily divided into 3 phases: inflammatory, proliferative, and remodeling. In reality, these 3 phases overlap significantly, and signaling cascades initiated in 1 phase influence cell growth and differentiation in later phases.

Inflammatory phase. Immediately after wounding, platelets and the coagulation cascade initiate primary and secondary hemostasis. During primary hemostasis, platelets release numerous cytokines, including transforming growth factor-β (TGF-β), which trigger the subsequent production of additional growth factors, such as basic fibroblast growth factor 2, from nearby cells. The fibrin mesh scaffold established during secondary hemostasis acts as a reservoir for growth factors and provides a matrix for future tissue deposition. In addition, cellular membrane-bound receptors, such as intercellular adhesion molecule 1 (ICAM-1), facilitate recruitment of inflammatory cells. Within minutes of injury, neutrophils arrive. Then, over the course of 2 to 3 days, macrophages become predominant. Treatment with the corticosteroid dexamethasone decreases the expression of cytokines, including TGF-β1, platelet-derived growth factor, tumor necrosis factor, and interleukin-1α in wounded tissue and may thereby decrease the chemotactic and mitogenic stimulus for other inflammatory cells. Dexamethasone also downregulates endothelial cell expression of intercellular adhesion molecule 1 (ICAM-1) in culture and in healing colonic anastomoses, resulting in attenuated granulocyte adhesion and migration. Consistent with this finding, high-dose corticosteroids reduce the extent of macrophage infiltration into the wound.

Proliferative phase. Platelets and macrophages from the inflammatory phase establish the growth factor and cytokine milieu that drives angiogenesis, fibroplasia, and re-epithelialization during the proliferative phase. Following construction of the framework of extracellular matrix and new blood vessels, epithelial cells from the basal layer migrate across the basal lamina. Re-epithelialization, stimulated by keratinocyte growth factor (KGF), is also dependent upon plasmin and matrix metalloproteinases to digest the leading edge of the fibrin clot. Corticosteroids reduce TGF-β levels and mesenchymal cell expression of keratinocyte growth factor (KGF), which attenuates fibroblast proliferation and impairs wound re-epithelialization.

Remodeling phase. During remodeling, the wound undergoes contraction and alters its collagen expression pattern. Myofibroblasts facilitate wound contraction via TGF-β1 stimulation. Collagen remodeling requires collagen digestion and a switch from type III collagen in the wound to type I collagen. Animal studies suggest that corticosteroids impair collagen turnover, disrupt dermal–epidermal junctional interactions, and decrease the tensile strength of cutaneous wounds by reducing collagen accumulation.

Notably, the mechanisms described above occur in the setting of acute wound healing, but corticosteroids have systemic and possibly indirect effects as well, which are less well understood. Insights into these processes could promise new therapeutics, including steroids that retain anti-inflammatory properties but have minimal adverse effects on wound healing.

Clinical effects of corticosteroids on wound healing

In the same year that Hench et al described their “medical miracle,” Ragan et al documented impaired wound healing in 3 of 8 rheumatoid arthritis patients treated with 25 U/day of adrenocorticotropic hormone (roughly equivalent to 75 mg/day of prednisone). Specifically, these patients developed a nonhealing biopsy site, a nonhealing episiotomy site and decubitus ulcer, and nonhealing abscess drainage sites. In 2 of these patients, the wounds quickly granulated within 4 days of discontinuing adrenocorticotropic hormone treatment. These findings led to subsequent studies to better evaluate the effects of corticosteroids on wound healing. Below, data from animal models, patients with Cushing syndrome, and clinical studies are reviewed.
Effect of corticosteroid dose on wound healing

A number of animal studies have quantified the effects of high-dose corticosteroids on wound tensile strength and anastomotic bursting pressures (Table 1). Comparing these animal studies as a group is challenging because of differences in methodology, internal controls, and measurement of wound strength. Overall, these studies converge on an approximately 30% reduction in wound tensile strength at cortisone doses of 15 to 40 mg/kg/day, equivalent to approximately 200 to 560 mg/day of prednisone in a 70-kg person (Table 1), but these results cannot be generalized to other species. For example, cortisone dramatically decreases wound tensile strength in rats but has no effect at equivalent doses in guinea pigs. Indeed, human studies should ultimately provide evidence for clinical decision making.

Patients with Cushing syndrome are chronically exposed to excess adrenocorticoids and provide the closest human correlate to these animal studies. Compared with a healthy human population, 5 patients with Cushing syndrome demonstrated a 40% reduction in cutaneous wound tensile strength. Notably, 1 patient’s tensile strength improved after adrenal resection. These findings suggest that corticosteroid excess may adversely affect wound healing in humans; however, these patients are chronically exposed to high doses of cortisol, whereas in clinical practice, the doses are usually smaller and may be given on an acute or chronic basis. Additionally, although a retrospective case series described increased wound complication rates in patients with Cushing syndrome, the absolute risk appeared to be small, even with open procedures requiring large incisions. Furthermore, wound disruption or dehiscence, rather than wound tensile strength, should be considered more clinically relevant outcome measures.

Effect of chronicity of corticosteroid administration on wound healing

Since the duration of systemic corticosteroid exposure may affect wound healing, the effects of acute and chronic corticosteroid administration are compared below for various indications.

Acute administration. The inflammatory response that occurs shortly after myocardial infarction is analogous to creation of an acute wound that heals over the course of days to weeks; thus, limiting the extent of postinfarct inflammation may improve subsequent outcomes. Initial studies performed in the 1960s and 1970s yielded conflicting results. Some studies suggested as much as a 50% mortality reduction with high-dose cortisone, while others suggested no benefit on mortality or an increase in myocardial infarction (MI) extent and higher risk of ventricular aneurysm. In all of these studies in which initiation of treatment ranged from within 6 to 72 hours after symptom onset, a large dose of prednisone (100 mg/day) for at least 10 days was required for a therapeutic or toxic effect. In 2003, a meta-analysis of high-dose corticosteroids at the time of myocardial infarction (MI) suggested a slight decrease in mortality associated with high-dose corticosteroids, but the result was statistically insignificant when considering randomized controlled trials only. More recently, a Cochrane review of 54 randomized studies concluded that prophylactic corticosteroids in adult cardiac surgery patients provide no mortality benefit. Importantly, the

Table 1 Effect of acute corticosteroid administration on wound tensile strength in animals

<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>Animal</th>
<th>Drug</th>
<th>Dose (mg/kg/day)</th>
<th>Wound type</th>
<th>Outcome measure</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howes et al, 1950</td>
<td>Rat</td>
<td>C</td>
<td>40</td>
<td>I</td>
<td>TS</td>
<td>−38</td>
</tr>
<tr>
<td>Findlay &amp; Howes, 1952</td>
<td>Rabbit</td>
<td>C</td>
<td>1.5</td>
<td>I</td>
<td>TS</td>
<td>0</td>
</tr>
<tr>
<td>Meadows &amp; Prudden, 1953</td>
<td>Rat</td>
<td>C</td>
<td>4, 20, 100</td>
<td>I</td>
<td>BD</td>
<td>−30, −36, −65</td>
</tr>
<tr>
<td>Pearce et al, 1969</td>
<td>Rat</td>
<td></td>
<td>20</td>
<td>I</td>
<td>TS</td>
<td>−45</td>
</tr>
<tr>
<td>Hinshaw et al, 1961</td>
<td>Rabbit</td>
<td>C</td>
<td>12.5</td>
<td>I</td>
<td>BD</td>
<td>0</td>
</tr>
<tr>
<td>Sandberg, 1964</td>
<td>Rat</td>
<td>C</td>
<td>40</td>
<td>I</td>
<td>TS</td>
<td>−30</td>
</tr>
<tr>
<td>Ehrlich &amp; Hunt, 1968</td>
<td>Rat</td>
<td>C</td>
<td>25</td>
<td>I</td>
<td>TS</td>
<td>−30</td>
</tr>
<tr>
<td>McNamara et al, 1969</td>
<td>Rat</td>
<td>Dex</td>
<td>6</td>
<td>I</td>
<td>TS</td>
<td>0</td>
</tr>
<tr>
<td>Dostal &amp; Gamelli, 1990</td>
<td>Mouse</td>
<td>Dex</td>
<td>16</td>
<td>I</td>
<td>TS</td>
<td>−59</td>
</tr>
<tr>
<td>Dostal &amp; Gamelli, 1990</td>
<td>Mouse</td>
<td>C</td>
<td>400</td>
<td>I</td>
<td>TS</td>
<td>−68</td>
</tr>
<tr>
<td>Dostal &amp; Gamelli, 1990</td>
<td>Mouse</td>
<td>MP</td>
<td>80</td>
<td>I</td>
<td>TS</td>
<td>0</td>
</tr>
<tr>
<td>Aszodi &amp; Ponsky, 1984</td>
<td>Rat</td>
<td>C</td>
<td>5</td>
<td>A</td>
<td>BP</td>
<td>−24</td>
</tr>
<tr>
<td>Cali et al, 1993</td>
<td>Rat</td>
<td>C</td>
<td>5</td>
<td>A</td>
<td>BP</td>
<td>0</td>
</tr>
<tr>
<td>Mastboom et al, 1991</td>
<td>Rat</td>
<td>MP</td>
<td>2.5, 10</td>
<td>A</td>
<td>BP</td>
<td>0, 0</td>
</tr>
<tr>
<td>Phillips et al, 1992</td>
<td>Rabbit</td>
<td>Dex</td>
<td>0.1</td>
<td>A</td>
<td>BP</td>
<td>−46</td>
</tr>
<tr>
<td>Furst et al, 1994</td>
<td>Rat</td>
<td>C</td>
<td>15</td>
<td>A</td>
<td>BP</td>
<td>−33</td>
</tr>
</tbody>
</table>

In all of these studies, animals were given corticosteroids within 1 week prior to surgery and then daily after surgery until the time of outcome measure determination. In each case, the outcome measure was determined within 7 days after wounding.

A = anastomosis; BD = balloon disruption; BP = bursting pressure; C = cortisone; Dex = dexamethasone; I = incision; MP = methylprednisolone; TS = tensile strength.
authors noted no significant increase in postoperative infection or impairment of wound healing.

Likewise, patients with suspected temporal arteritis may receive corticosteroids (usually 40 to 60 mg/day of prednisone) shortly before undergoing temporal artery biopsy. In a large case series of patients with suspected temporal arteritis, 237 individuals underwent 250 temporal artery biopsies.54 Corticosteroids were given to 178 (75%) of these patients preoperatively, with a mean preoperative duration of 7.3 ± 2.0 days. There were no biopsy-related complications.54 More recently, Younge et al55 reviewed the records of 1,113 patients who underwent temporal artery biopsy for suspected temporal arteritis. Twenty percent of these patients were on corticosteroid therapy at the time of the procedure, but none experienced serious complications.55 Other case series in the literature have not reported the complication rate, if any, of temporal artery biopsy and its relationship to preoperative prednisone administration.

To date, only 1 randomized, double-blind, placebo-controlled trial has addressed the effects of acute, preoperative corticosteroid administration on cutaneous wound healing.56 In this study of 24 patients, a single dose of 30 mg/kg methylprednisolone or placebo was administered intravenously 90 minutes prior to colon resection. Among the 12 patients in the treatment group, only 1 patient developed a wound dehiscence, while 2 patients in the placebo group developed a dehiscence. No wound infections occurred in the treatment group, but 1 infection required surgical debridement in the placebo group. For direct tissue evaluation, a small subcutaneous wound was created on each patient’s upper arm. Proline levels in the collagen and the amount of collagen accumulation within the wounds over 10 postoperative days were evaluated. The authors found no difference between the treatment and control groups.56 This study suggests that acute, high-dose steroid administration does not significantly affect wound healing, as measured by both clinical and biochemical parameters.

Perioperative “stress dosing” with physiologic or supraphysiologic levels of corticosteroids in patients on chronic corticosteroids is beyond the scope of this article and has been reviewed recently elsewhere.57,58 It is worth noting, however, that these reviews did not report an increased risk of wound dehiscence or infection.

Taken together, these data, although limited, suggest that acute, high-dose corticosteroid administration for less than 10 days has no clinically important effect on wound healing.

Chronic administration. Only a few human studies have quantified the risks of corticosteroid-induced wound complications in surgical practice (Table 2).59–62 These studies found that rates of wound complications may be increased 2- to 5-fold in patients taking corticosteroids compared with those not on corticosteroids; however, since the majority of the studies were uncontrolled and retrospective, it is difficult to determine whether the complications were confounded by other factors.

### Table 2 Effect of chronic corticosteroid administration on wound healing in humans

<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>N</th>
<th>Equivalent dose (mg/day of prednisone)</th>
<th>Duration</th>
<th>Wound complication rate (control %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Numerous Diseases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green, 196561</td>
<td>38</td>
<td>10.8 ± 7</td>
<td>1 day–13 mo</td>
<td>29 (NR)</td>
</tr>
<tr>
<td>Engquist et al, 197460</td>
<td>100</td>
<td>18 pts: &lt;10</td>
<td>19 pts: &lt;1 yr</td>
<td>44 (22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>74 pts: &gt;10</td>
<td>73 pts: &gt;1 yr</td>
<td></td>
</tr>
<tr>
<td>Reding et al, 199662</td>
<td>55</td>
<td>51 (15–480)</td>
<td>18 mo</td>
<td>13 (2)</td>
</tr>
<tr>
<td><strong>Rheumatoid Arthritis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Popert &amp; Davis, 195868</td>
<td>15</td>
<td>12.4 ± 3</td>
<td>25 ± 16 mo</td>
<td>20</td>
</tr>
<tr>
<td>Garner et al, 197365</td>
<td>100</td>
<td>2.5–15</td>
<td>Variable</td>
<td>71 (25)</td>
</tr>
<tr>
<td>Escalante &amp; Beardmore, 199556</td>
<td>204</td>
<td>6.4 ± 2.2</td>
<td>NR</td>
<td>15.9</td>
</tr>
<tr>
<td>Jain et al, 200267</td>
<td>30</td>
<td>8.8 (4.25–20)</td>
<td>NR</td>
<td>3.3 (9.5)</td>
</tr>
<tr>
<td><strong>Inflammatory Bowel Disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Price, 196874</td>
<td>80</td>
<td>NR</td>
<td>NR</td>
<td>15 (40)</td>
</tr>
<tr>
<td>Knudsen et al, 197672</td>
<td>41</td>
<td>&gt;40</td>
<td>NR; &gt;2 mo</td>
<td>66 (27)</td>
</tr>
<tr>
<td>Allsop &amp; Lee, 197669</td>
<td>162</td>
<td>&gt;20</td>
<td>NR</td>
<td>31</td>
</tr>
<tr>
<td>Post et al, 199173</td>
<td>265</td>
<td>NR</td>
<td>NR; preoperative</td>
<td>19 (7)*</td>
</tr>
<tr>
<td>Ziv et al, 199675</td>
<td>361</td>
<td>169 pts: &gt;20</td>
<td>NR; &gt;1 mo</td>
<td>8 (6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>192 pts: &lt;20</td>
<td></td>
<td>12 (6)</td>
</tr>
<tr>
<td>Bruewer et al, 200370</td>
<td>219</td>
<td>73 pts: &gt;20</td>
<td>NR</td>
<td>18 (11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>146 pts: &lt;20</td>
<td>NR</td>
<td>12 (11)</td>
</tr>
</tbody>
</table>

N is the number of patients or the number of operations from each study in the experimental group. Dose is adjusted for equivalent doses of prednisone (1 = 1 mg/day prednisone). Duration refers to the number of months that patients took corticosteroids preoperatively. Wound complication rate is defined as disruption, persistent drainage, dehiscence, infection, or wound failure. In cases where no control group was included, there are no parenthetical numbers provided. *Indicates there was a statistically significant difference in complication rates between the experimental and control groups. NR = not reported; pts = patients.
Similarly, a recent retrospective study reviewed the National Surgical Quality Improvement Program public use files from 2005 to 2008 to evaluate the adverse effects of preoperative corticosteroid use. The authors found that of the 635,265 patients identified in the database, the 20,434 patients (3.2%) who were treated with chronic parenteral or oral corticosteroids for at least 30 days prior to surgery had a significant increase in rates of superficial and deep surgical site infections (from 2.9% to 5% and from 0.8% to 1.8%, respectively) with steroid use. They also reported a 2- to 3-fold increase in wound dehiscence and a 4-fold increase in mortality associated with preoperative corticosteroid use; however, the authors were unable to specify the dose or duration of corticosteroid use and the underlying condition that required corticosteroid therapy, which may have contributed to the increased complication rates. In addition, they did not identify the types of surgery performed or address whether corticosteroids were continued postoperatively.

The orthopaedic literature has also provided a few studies regarding wound healing in patients with rheumatoid arthritis (RA; Table 2). Poss et al retrospectively found that RA patients have a 2- to 3-fold greater risk of infection and wound complications after joint replacement compared with patients with osteoarthritis undergoing similar procedures. A larger study of 100 RA patients suggested that patients taking corticosteroids for more than 3 years had statistically significantly delayed wound healing after surgery compared with those taking corticosteroids for fewer than 3 years. Additionally, in a retrospective study of 204 RA patients who underwent joint surgery, the authors noted a dose-dependent trend toward increased complication rates associated with corticosteroid administration, but the differences were not statistically significant. Similarly, during 30 hand and wrist procedures in 18 patients taking an average of 8.8 mg/day of prednisone, only 1 wound dehiscence occurred; there were no other wound complications in the steroid-treated group. In contrast, another report of 15 RA patients undergoing surgery while taking cortisone (at doses equivalent to 12.5 to 20 mg/day of prednisone for between 2 weeks and 57 months) described no significant corticosteroid effect on wound healing, except in a few cases associated with overt signs of hypercortisolism. Altogether, corticosteroid administration appears to increase the risk of wound complications in RA patients, but not all data have been statistically significant. Furthermore, because these studies were not randomized, it is unclear whether the increased risk is related to intrinsic disease activity, restrictions on postoperative mobility, the effects of other medications used for RA, or corticosteroid effects alone.

In patients with inflammatory bowel disease, retrospective clinical studies have also reported conflicting results (Table 2). Some studies showed no significant increase in postoperative wound complications, while others reported greater risk of wound infection, anastomotic leakage, intra-abdominal abscesses, and sepsis associated with preoperative corticosteroids. For example, chronic corticosteroid use was associated with a greater than 3-fold increased infection rate in patients with inflammatory bowel disease undergoing bowel resection, with even higher infection rates occurring at doses of prednisone greater than 40 mg/day. In addition, some studies have suggested that corticosteroid administration in patients with concomitant intestinal abscesses greatly increases the risk of postoperative morbidity.

Although patients with primary nonmalignant dermatologic diseases do not typically undergo surgical procedures for their skin conditions, some have chronic wounds that present significant treatment challenges. Pyoderma gangrenosum is an uncommon neutrophilic dermatosis characterized by tender ulcers, often on the lower extremities or at sites of trauma, with bluish undermined borders and surrounding erythema. These lesions may develop in association with systemic diseases, such as inflammatory bowel disease, rheumatologic disease, or hematologic malignancies, but approximately 25% to 50% of cases are idiopathic. The treatment of choice for this condition is systemic corticosteroids (0.5 to 2 mg/kg per dose, generally 40 to 60 mg/day) for at least 4 to 6 weeks, sometimes requiring multiple courses because of recurrence. For refractory disease, high-dose intravenous methylprednisolone (1,000 mg/day) has been used for pulse therapy. Topical corticosteroids (such as high-potency clobetasol propionate 0.05%) and intralesional corticosteroids are also considered options, although there is some concern for pathergy with the latter. In these cases, suppression of the underlying inflammatory process with corticosteroids facilitates ulcer healing. Surgical treatment, such as debridement, would exacerbate the condition.

Perhaps the most convincing evidence regarding the effects of chronic, high-dose corticosteroids on wound healing is the previously cited example of Cushing syndrome. These effects are similar to those that Ragan et al observed. Granted, both are examples of high-dose and chronic exposure, whereas the key clinical question is the effect of low-dose but chronic corticosteroids.

Altogether, the clinical data discussed above suggest that preoperative corticosteroid treatment of at least 30 days, particularly at prednisone doses of 40 mg/day or greater, may increase wound complication rates by up to 2 to 5 times compared with patients not on corticosteroids. Some patients, such as those with RA, may be more susceptible to wound complications as well. Nevertheless, corticosteroids still play a significant role in facilitating wound healing in other conditions, such as pyoderma gangrenosum.

Effect of timing of corticosteroid administration on wound healing

Postoperative timing of administration may be critical, as in the case of a patient who develops an acute flare...
of gout postoperatively and requires corticosteroids for alleviation of pain. Animal studies have suggested that corticosteroids have no effect on wound tensile strength if administered 3 or more days after wounding.27 If given in large doses, however, postoperative corticosteroids could cause immunosuppression and predispose to infection, which in turn contributes to mechanical complications of wound healing. To our knowledge, no clinical studies have compared the differential effects of corticosteroids on wound healing when given before versus after surgery.

Summary

To better manage patients on corticosteroids, the optimal dose and duration that will minimize the adverse effects on wound healing while still adequately treating the underlying condition need to be determined. If the dose and chronicity are defined in relation to hypothalamic–pituitary–adrenal axis suppression, then administration lasting less than 5 days could be considered “acute,” and doses greater than 10 mg/day for more than 1 week might be considered “chronic.”81 Although it is not clear whether hypothalamic–pituitary–adrenal suppression is in any way related to altered wound healing, these numbers estimate the endogenous levels of corticosteroids produced under physiologic conditions. Any dose lower than these values is unlikely to have pharmacologic effects. Regarding timing of administration, animal studies have shown that corticosteroids given at least 3 days after wounding have no effect on wound healing.27 Altogether, these findings suggest that there are no contraindications to prescribing a short course of corticosteroids (eg, 5 mg/day of prednisone for 5 to 10 days), for example, to a postoperative patient suffering from an acute flare of gout if initiated at least 3 days after surgery. Certainly, large prospective, randomized, controlled trials are needed to fully address this issue.

Establishing an optimal corticosteroid dose and duration is challenging for several reasons. First, the mechanisms whereby corticosteroids impair wound healing are incompletely understood. In particular, impairment of wound healing associated with chronic corticosteroid use and in patients with Cushing syndrome underscores the need to better understand the systemic and indirect effects of corticosteroids. Additionally, different corticosteroids may have varying tissue concentrations or affinity for the molecular targets that influence wound healing. Moreover, dosing and duration should also be tailored toward the individual patient with attention to the underlying condition requiring corticosteroids and any comorbidities. Smaller procedures, such as temporal artery biopsies, are expected to have lower wound complication rates than larger procedures, such as bowel resection with anastomotic reconstruction. Thus, the type of surgery and the patient’s clinical status would likely further influence considerations for perioperative corticosteroids and alter the overall risk of wound complications.

Conclusions

More than 50 years after their miraculous introduction to clinical medicine, corticosteroids are still commonly used and effective therapies for numerous inflammatory disorders. Although wound disruptions have occurred in patients taking corticosteroids, in clinical practice, treatment doses are generally below the level required for dramatic inhibition of wound healing. In the absence of large prospective randomized controlled studies, this question remains incompletely answered.

Now, corticosteroid research is moving toward dissociating the anti-inflammatory effects of corticosteroids from their numerous side effects with the development of so-called selective glucocorticoid receptor modulators.28,82 Some reports have suggested that methylprednisolone may have less effect on wound healing than other corticosteroids,16 but these results require confirmation.

Several strategies have also emerged to mitigate the effects of corticosteroids on wound healing. These approaches include local administration of vitamin A and cytokine modulation.83 For decades, vitamin A has been known to reverse the effects of corticosteroids on wound healing in animals; this approach is sometimes used in humans but has never been validated in a controlled study of wound complication rates.17,84–86 Additionally, cytokine modulation, such as with the use of TGF-β, may be an exciting mechanism for counteracting corticosteroid effects on wound healing but requires further investigation.87,88

Overall, corticosteroids have been and will likely continue to be essential components of our pharmacologic armamentarium. Therefore, until more data become available to guide clinical practice, appropriate preoperative patient counseling about the potential risks of impaired wound healing would be prudent.

References


