

Rational Use of Perioperative Corticosteroid Supplementation in Patients at Risk for Acute Adrenal Insufficiency

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Soon after cortisone was introduced into the therapeutic arsenal in the late 1940s, Fraser et al¹ reported a case of fatal postoperative adrenal insufficiency in a 34-year-old man with rheumatoid arthritis chronically treated with cortisone. The patient underwent hip arthroplasty, and cortisone was withheld for 2 days preoperatively. Although the intraoperative course was uneventful, immediately after surgery the patient developed hypotension refractory to volume expansion, vasopressors, and the administration of “adrenal cortical extract.”¹ He died 3 hours postoperatively. The autopsy was notable for marked atrophy of the adrenal glands.

Recommendations for perioperative use of supplemental corticosteroids were published soon after this case report^{2,3} and became the standard of care for several decades. These early recommendations, which were based on anecdotal evidence and an incomplete understanding of the hypothalamic-pituitary-adrenal (HPA) axis and its response to physiologic stress, called for 200 to 400 mg of hydrocortisone in the 24 hours following surgery with a 2- to 4-week taper. Although early guidelines effectively prevented acute adrenal insufficiency, the excessive duration and dosages of corticosteroid therapy increased the risk for infection due to hyperglycemia⁴ and immunosuppression and delayed wound healing.⁵ An improved understanding of the HPA axis and the variables that influence the risk for postoperative adrenal crisis in corticosteroid-treated patients has led to a reevaluation of these early recommendations. Although the evidence remains limited, it supports recommendations for lower dosages and a shorter duration of corticosteroid therapy.^{6,7}

This article outlines a rational approach to the use of perioperative corticosteroid supplementation in patients at risk for acute adrenal insufficiency, which is based on current evidence. Although most causes of adrenal insufficiency are rare, chronic systemic corticosteroid therapy—the most common cause of adrenal

insufficiency—remains a mainstay of therapy for a wide variety of diseases, such as chronic obstructive pulmonary disease and rheumatoid arthritis. Thus, a broad range of physicians (internists, family practitioners, medical subspecialists, anesthesiologists, surgeons) are responsible for managing patients potentially at risk for postoperative adrenal crisis. Appropriate use of corticosteroid supplementation relies on the ability to identify patients at risk and an understanding of the normal response of the HPA axis to surgical stress.

HPA AXIS: NORMAL PHYSIOLOGY AND RESPONSE TO SURGICAL STRESS

The adrenal cortex synthesizes and secretes steroid hormones (glucocorticoids, mineralocorticoids, sex steroids) that are essential to life. In humans, the most important glucocorticoid hormone is cortisol (also known as hydrocortisone). In addition to immunologic and metabolic effects, cortisol plays an important role in maintaining vascular tone. Glucocorticoids are important for normal adrenal epinephrine and norepinephrine production⁸ as well as for facilitating the full vasoconstrictive effects of catecholamines.⁹ As highlighted by Fraser’s classic case report, volume resuscitation and vasopressor therapy with catecholamines are less effective in the absence of cortisol.

Cortisol Production

Production and secretion of cortisol by the adrenal cortex is regulated primarily by pulsatile release of adrenocorticotropic hormone (ACTH) from the

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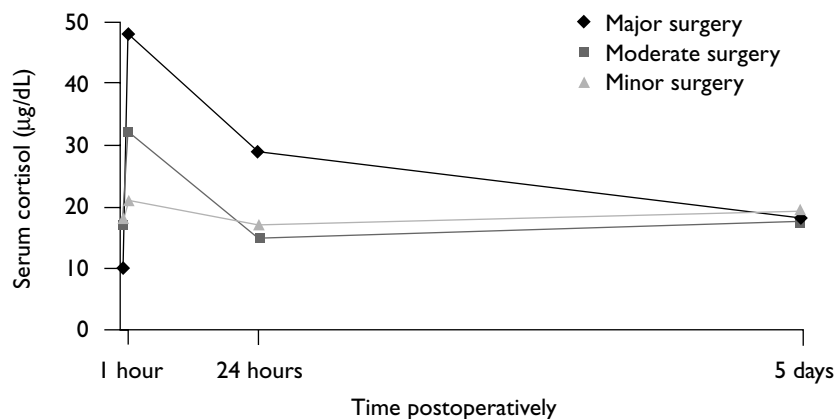


Figure 1. Serum cortisol response to graded surgical stress. Time points shown are baseline and 1 hour, 24 hours, and 5 days postoperatively. (Data from Chernow B, Alexander HR, Smallridge RC, et al. Hormonal responses to graded surgical stress. *Arch Intern Med* 1987;147:1273–8.)

anterior lobe of the pituitary, which in turn is regulated by synthesis and secretion of corticotropin-releasing hormone (CRH) by the hypothalamus—thus forming the HPA axis. A diurnal variation in cortisol release exists, with serum levels peaking in the early morning. Both ACTH and CRH are inhibited by cortisol in a classic negative feedback loop. Prolonged suppression of ACTH may lead to adrenocortical atrophy.

Basal production. Original estimates of basal cortisol production in humans were approximately 20 to 25 mg/day. However, a more recent study of 12 healthy volunteers using a novel method of endogenous cortisol measurement (ie, stable isotope dilution/mass spectrometry) found the mean production of cortisol to be approximately 10 mg/day.¹⁰ This study suggests that earlier estimates of basal cortisol production were grossly inflated.

Impact of stress. Acute stress activates the HPA axis, resulting in a rapid but short-lived spike in serum cortisol levels. Cortisol production under stressful conditions, such as major surgery, has been evaluated by several investigators using a variety of techniques.^{11–18} These estimates have ranged widely due to individual variation in cortisol secretion in response to stress as well to the methodologic differences in the studies. However, it is now generally accepted that normal individuals produce 75 to 150 mg/day of cortisol in response to major surgical stress and rarely produce more than 200 mg of cortisol in the 24 hours following major surgery.⁶

It previously was shown that the rise in serum cortisol concentrations parallels the severity of medical illness or trauma.^{19–23} Chernow et al²⁴ hypothesized that the endogenous HPA response also should correlate with the magnitude of surgical stress. The HPA response of patients scheduled for elective surgery was studied prospectively through the perioperative period. Patients were stratified by the type of surgery:

1) minimal stress procedures (eg, inguinal herniorrhaphy); 2) moderate stress procedures (eg, cholecystectomy); and 3) severe stress procedures (eg, colectomy). Hemodynamic parameters and serial evaluations of hormone levels, including cortisol, were collected at baseline and at 1 hour, 24 hours, and 5 days postoperatively. Patients who underwent minor procedures had no significant changes from baseline in hemodynamics or serum cortisol levels (**Figure 1**). Cortisol levels were significantly elevated 1-hour postoperatively in patients who underwent moderate and severe surgical procedures. Sustained elevation of serum cortisol levels at 24 hours occurred only in the severe surgical stress group and returned to baseline by 5 days in this group. Thus, the endogenous response of the HPA axis during surgical stress correlates to the intensity of the procedure and is short-lived (< 24 hours), except in patients undergoing major surgery.

Causes of Decreased Cortisol Production

Numerous conditions can disrupt normal HPA function and lead to inadequate cortisol production (adrenal insufficiency). Causes of adrenal insufficiency may be classified as *primary* (adrenal gland destruction or dysfunction), *secondary* (pituitary gland dysfunction or destruction), or *tertiary* (hypothalamic dysfunction or destruction). Because of the widespread use of glucocorticoid therapy, suppression of the HPA axis by exogenous systemic corticosteroids is the most common cause of adrenal insufficiency. High dosages of inhaled corticosteroids can cause some degree of adrenal suppression.²⁵ Although clinically relevant adrenal suppression due to inhaled corticosteroids is unlikely to occur in the perioperative setting, it is important to be aware of the possibility. Other medications that inhibit glucocorticoid synthesis (eg, ketoconazole) or increase glucocorticoid metabolism (eg, phenytoin, rifampin) may precipitate

adrenal crisis in patients with diminished adrenal reserve due to coexisting primary adrenal disease or hypothalamic-pituitary disease.

HPA Response to Surgical Stress in Corticosteroid-Treated Patients

Although frequently discussed and much feared, it is important to recognize that the incidence of postoperative adrenal crisis is quite low (approximately 0.01%–0.7% in more than 70,000 patients).^{26–29} Acute life-threatening postoperative adrenal crisis is rare even in patients receiving chronic corticosteroid therapy who undergo major surgery without glucocorticoid supplementation, as was revealed in a study by Kehlet and Binder.³⁰ These authors prospectively studied patients receiving chronic corticosteroid therapy who were scheduled for major or minor elective surgical procedures. Corticosteroid therapy was abruptly discontinued 36 hours before surgery and restarted 72 hours after major procedures (eg, colectomy) and 24 hours after minor procedures (eg, hemorrhoidectomy). The patients received no perioperative corticosteroid supplementation. Surprisingly, no patients died and only 7 of 74 patients undergoing major surgical procedures and 1 of 30 undergoing minor surgery experienced hypotension; of the 8 patients who experienced hypotension, only 1 required corticosteroid treatment to reverse the hypotension. All others responded to volume expansion with intravenous fluids. Thus, only 1 of 104 patients on chronic corticosteroid therapy had potentially life-threatening adrenal insufficiency when prophylactic perioperative corticosteroids were withheld.³⁰ Although numerous case reports of postoperative hypotension and death in patients receiving chronic exogenous glucocorticoids exist, most of these cases lack definitive biochemical confirmation of the diagnosis.³¹ Despite its relative infrequency, postoperative adrenal insufficiency merits attention as a preventable cause of morbidity and mortality.

Evidence that inadequate corticosteroid supplementation leads to adverse perioperative outcomes is provided by a study of nonhuman primates.³² In this study, cynomolgus monkeys were adrenalectomized and placed on physiologic replacement dosages of glucocorticoid and mineralocorticoid for a 4-month recovery period. Control subjects underwent a sham adrenalectomy (abdominal surgery without organ removal). Following the recovery period, the adrenalectomized monkeys were stratified into 3 groups receiving varying replacement dosages of corticosteroid for 4 days: 1) one tenth physiologic dosage; 2) physiologic dosage; and 3) ten times physiologic dosage. All monkeys then un-

derwent a cholecystectomy. The monkeys who received the subphysiologic dosage had a significant increase in mortality as compared with the control group (38% versus 0% mortality; $P < 0.05$). A significant increase in perioperative hemodynamic compromise (hypotension, decreased systemic vascular resistance, and decreased left ventricular work index) also was noted in the subphysiologic replacement group as compared with the physiologic and supraperphysiologic replacement groups. Interestingly, no differences were noted between the group on physiologic replacement and the group on supraperphysiologic replacement, leading the authors to conclude that supraperphysiologic dosages of glucocorticoids offered no apparent advantage during surgical stress in primates.

APPROACH TO PERIOPERATIVE CORTICOSTEROID SUPPLEMENTATION

Preoperative Assessment: Is this Patient at Risk for Adrenal Crisis?

The first step in evaluating patients preoperatively is to identify those at high risk for adrenal insufficiency. While patients with known primary adrenal insufficiency (eg, Addison's disease) or secondary adrenal insufficiency (eg, pituitary macroadenoma) certainly are at risk, these causes are uncommon. Suppression of the HPA axis by exogenous glucocorticoids is a much more common clinical scenario. In addition to asking about present or past use of corticosteroids, the physician should be vigilant in pursuing an explicit medication history because patient-reported information often is inaccurate and incomplete.³³ Obtaining a medication history is particularly important for patients who have diseases that commonly require long-term corticosteroid therapy, such as rheumatoid arthritis or chronic obstructive pulmonary disease. To properly assess the need for perioperative corticosteroid supplementation in a patient with a current or past history of corticosteroid therapy, it is imperative to know the following: 1) what dosage of chronic corticosteroid therapy suppresses the HPA axis; 2) what duration of short-term corticosteroid therapy suppresses the HPA axis; and 3) how long the HPA axis remains suppressed after long-term corticosteroid treatment.

What dosage of chronic corticosteroid therapy suppresses the HPA axis? Adrenal function was assessed by the ACTH stimulation test in a cohort of patients in a rheumatology clinic who were receiving 1.5 to 10 mg/day of prednisone.³⁴ The investigators found that no patient receiving less than 5 mg/day of prednisone had a suppressed HPA axis. Several prior studies have reported similar findings.^{35–37} Based on these

Table 1. Glucocorticoid Equivalencies

Glucocorticoid	Potency	Dosage Equivalent	Biologic Half-life, hour
Hydrocortisone	1	20 mg	24–36
Prednisone	4	5 mg	24–36
Methylprednisolone	5	4 mg	24–36
Dexamethasone	30	0.75 mg	> 48

Adapted with permission from Axelrod L. Glucocorticoid therapy. *Medicine (Baltimore)* 1976;55:39–65.

studies, any patient who is taking at least 5 mg/day of prednisone (or an equivalent dosage of another glucocorticoid; **Table 1**) is at risk for postoperative adrenal crisis and should be considered for perioperative corticosteroid supplementation.

What duration of short-term corticosteroid therapy suppresses the HPA axis? Streck and Longwood³⁸ administered 25 mg of prednisone twice daily to 10 healthy volunteers for 5 days. Blunted response to ACTH stimulation was noted up to 5 days after the last dose of exogenous corticosteroid. Henzen et al³⁹ evaluated patients who had received 5 to 30 mg/day of prednisone for 5 to 30 days after glucocorticoids were discontinued. Low-dose corticotropin stimulation testing (1/250th the dose of ACTH used for standard testing) revealed that 34 of 75 patients had suppressed adrenal responses. The patients with suppressed adrenal responses were followed with serial low-dose corticotropin stimulation testing; after 2 weeks, 94% (32 of 34 patients) had normalized, and the remaining 2 patients stayed suppressed for 3 and 6 months, respectively.³⁹ Thus, patients who have received corticosteroid (≥ 5 mg/day of prednisone) for 5 days or more within the past 2 weeks should be considered at risk for acute postoperative adrenal insufficiency. A minority of patients may remain at risk for several months. Strategies for managing patients in this situation include: 1) empiric supplementation with corticosteroids; 2) ACTH stimulation testing prior to surgery to assess the HPA axis; or 3) alerting the surgeon and anesthesiologist to the potential for perioperative adrenal insufficiency and using supplemental corticosteroid only if hemodynamic instability is encountered.

How long does the HPA axis remain suppressed after long-term corticosteroid treatment? Data on this topic are limited, with the best information coming from 2 early studies. Graber et al⁴⁰ evaluated 14 patients with chronic (1–10 years) HPA axis suppression caused by either Cushing's syndrome or supraphysiologic dos-

ages of exogenous corticosteroids. Plasma corticosteroid and ACTH levels were monitored prospectively following removal of the tumor in cases of Cushing's syndrome or discontinuation of exogenous corticosteroids. Adrenal stimulation testing was not performed. In some patients, full recovery of adrenal function (defined as normalization of the basal plasma cortisol levels) took longer than 9 months.⁴⁰

Livanou et al⁴¹ studied patients who had been receiving high-dosage (defined as ≥ 10 mg/day of prednisone) or low-dosage (defined as ≤ 7.5 mg/day of prednisone) glucocorticoid therapy for either long duration (> 18 months) or short duration (< 18 months). The minimum duration of therapy for inclusion in this study was not reported. Cortisol levels as well as adrenal response to insulin-induced hypoglycemia were serially measured for 1 year after discontinuing glucocorticoid therapy. Substantial variability in recovery of normal responsiveness of the HPA axis was observed. It took 1 year for all patients to recover a normal HPA response to insulin-induced hypoglycemia. Thus, patients who have had chronically administered corticosteroids discontinued within the past year remain at risk for postoperative adrenal insufficiency.

Summary. Patients who are currently receiving at least 5 mg/day of prednisone or who have received sustained corticosteroid therapy within the past year are at higher risk for postoperative adrenal insufficiency and should be considered for empiric supplementation to prevent adrenal crisis. Patients who have received a short course (≥ 5 days) of corticosteroid therapy within the past 2 weeks also are at risk and may be empirically supplemented, have preoperative evaluation of the HPA axis by ACTH stimulation testing, or be closely monitored for hemodynamic instability with administration of corticosteroid on an as-needed basis.

Appropriate Coverage in High-Risk Patients: What Dosage and Duration?

When a patient is determined to be at risk for postoperative acute adrenal insufficiency and the decision is made to provide corticosteroid supplementation, the appropriate dosage and duration of coverage must be determined. At this point, it is important to consider the magnitude of the anticipated surgical procedure. **Table 2** summarizes our recommendations based on the available data and recent expert recommendations.^{6,7} There are no data to guide the choice of corticosteroid or the optimal route of delivery and dosing frequency.

Minor surgery. Examples of minor surgical procedures include inguinal hernia repair, superficial skin opera-

Table 2. Recommendations for Perioperative Corticosteroid Supplementation

Type of Surgical Procedure	Corticosteroid Supplementation
Minor (eg, inguinal herniorrhaphy, endoscopic or superficial)	If currently receiving corticosteroid, usual dose of corticosteroid should be given morning of surgery; may resume prior regimen the day after surgery If not currently receiving corticosteroid, a physiologic replacement dose should be given prior to surgery (eg, hydrocortisone 10 mg IV or 20–25 mg PO*)
Moderate (eg, intraabdominal, orthopedic, or neurologic procedure)	Hydrocortisone 25 mg IV (50 mg PO) preoperatively followed by 12.5–25 mg IV (25–50 mg PO) every 6–8 hours for the first 24–36 hours postoperatively Taper to prior regimen over 1–2 days
Major (eg, cardiothoracic, major vascular, or Whipple procedure)	Hydrocortisone 50 mg IV preoperatively and every 6–8 hours postoperatively for the first 24–36 hours Taper to prior regimen over 2–3 days

NOTE. Recommended dosages and duration of corticosteroid supplementation are based on available data and recent reviews.^{6,7} IV = intravenously; PO = orally.

*Other corticosteroids may be substituted at equivalent dosages as no data exist to suggest that any corticosteroid is superior. The reported oral bioavailability of hydrocortisone is variable.^{42–46} A conservative estimate of 50% bioavailability for oral hydrocortisone is used.

tions, and endoscopic procedures. For patients currently receiving corticosteroid therapy, the usual dose of corticosteroid should be given the morning of surgery; patients should then resume their usual corticosteroid dose the day after surgery. For patients not currently receiving corticosteroid, a physiologic replacement dose (hydrocortisone, 10 mg intravenously [IV] or 20–25 mg orally [PO]) should be given preoperatively. No further postoperative supplementation is required.

Moderate surgery. Examples include intraabdominal, orthopedic, urologic, and neurologic surgical procedures. For patients undergoing such surgery, the estimated dosage and duration of corticosteroid supplementation are presumed to be intermediate between minor and major surgical procedures. It is estimated that endogenous production of cortisol is 50 to 75 mg in the first 24 hours after surgery in individuals with an intact HPA axis. Therefore, patients at higher risk for acute perioperative adrenal insufficiency should be given the equivalent of 25 mg of hydrocortisone IV (50 mg hydrocortisone PO) immediately before a moderate surgery and 12.5 to 25 mg IV (25–50 mg PO) of hydrocortisone every 6 to 8 hours in the 24 to 36 hours following surgery. Corticosteroids should be tapered rapidly over the following 1 to 2 days to the preoperative regimen.

Major surgery. Examples include cardiothoracic surgery, major vascular procedures, and a Whipple procedure. Estimates of cortisol production in the 24 hours following major surgery have varied widely.^{11–17} A commonly accepted estimate of endogenous cortisol production is 100 to 150 mg in the 24 hours

following major surgery.¹⁸ The equivalent of 50 mg of hydrocortisone IV should be administered preoperatively and every 6 to 8 hours for 24 to 36 hours following surgery. The dosage should then be tapered to the prior regimen over the next 2 to 3 days. It is important to remember and to advise surgical colleagues that postoperative complications (eg, infection) may necessitate continued corticosteroid supplementation.

CONCLUSION

Although postoperative adrenal crisis is a relatively rare occurrence in patients receiving chronic exogenous corticosteroids, it is a preventable cause of perioperative morbidity and mortality. Early recommendations for perioperative corticosteroid coverage were effective in preventing postoperative adrenal insufficiency but were not based on physiology of the HPA axis and its response to surgical stress. Furthermore, the dosage and duration of corticosteroid supplementation traditionally used may lead to adverse postoperative outcomes such as infection and delayed wound healing. Current recommendations based on data accumulated over the past several decades emphasize lower, more physiologic replacement dosages with a rapid taper after the completion of surgery. **HP**

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