

Requirement of Perioperative Stress Doses of Corticosteroids

A Systematic Review of the Literature

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Objective: To determine the requirement for perioperative supplemental (stress) doses of corticosteroids in patients receiving long-term corticosteroid therapy and undergoing a surgical procedure. Corticosteroids are among the most commonly prescribed medications and will predictably result in suppression of the hypothalamic-pituitary-adrenal axis with long-term use. Patients receiving therapeutic dosages of corticosteroids frequently require surgery; these patients are almost universally treated with stress doses of corticosteroids during the perioperative period.

Data Sources: MEDLINE, EMBASE, Cochrane Register of Controlled Trials, and citation review of relevant primary and review articles.

Study Selection: Randomized controlled trials (RCTs) comparing stress doses of corticosteroids with placebo and cohort studies that followed up patients after surgery in which perioperative stress doses of corticosteroids were not administered.

Data Extraction: Data were abstracted on the study design, study size, study setting, patient population, dosage and duration of previous corticosteroid therapy, adrenal function testing results, surgical intervention, corticosteroid dosing regimen, intraoperative and postoperative hemodynamic profile, and incidence of adrenal crisis.

Data Synthesis: Nine studies met our inclusion criteria, including 2 RCTs and 7 cohort studies. These studies enrolled a total of 315 patients who underwent 389 surgical procedures. In the 2 RCTs, there was no difference in the hemodynamic profile between patients receiving stress doses of corticosteroids compared with patients receiving only their usual daily dose of corticosteroid. In the 5 cohort studies in which patients continued to receive their usual daily dose of corticosteroid without the addition of stress doses, no patient developed unexplained hypotension or adrenal crisis. One patient in each of the 2 cohort studies (5% and 1% of the cohort) in which the usual daily dose of corticosteroid was stopped 48 and 36 hours before surgery developed unexplained hypotension; both of these patients responded to hydrocortisone and fluid administration.

Conclusions: Patients receiving therapeutic doses of corticosteroids who undergo a surgical procedure do not routinely require stress doses of corticosteroids so long as they continue to receive their usual daily dose of corticosteroid. Adrenal function testing is not required in these patients because the test is overly sensitive and does not predict which patient will develop an adrenal crisis. Patients receiving physiologic replacement doses of corticosteroids owing to primary disease of the hypothalamic-pituitary-adrenal axis, however, require supplemental doses of corticosteroids in the perioperative period.

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IN 2001, MORE THAN 34 MILLION prescriptions were written in the United States for the 4 most commonly used oral corticosteroids.¹ Corticosteroids are prescribed for patients with a wide variety of autoimmune and inflammatory diseases, for patients with chronic obstructive pulmonary disease and asthma, and for recipients of organ transplants. Because of their chronic medical conditions, these patients frequently require both elective and emergency surgical procedures. It is generally believed that patients receiving long-term corticosteroid therapy require supplemental perioperative (stress) doses of

corticosteroids owing to the presumed suppression of the hypothalamic-pituitary-adrenal (HPA) axis.²⁻⁵ Furthermore, it is believed that failure to provide supplemental perioperative corticosteroid therapy will result in adrenal crisis.²⁻⁵ The potential danger of long-term corticosteroid use in surgical patients was first described by Fraser and colleagues in 1952.⁶ They described a corticosteroid-dependent patient undergoing major orthopedic surgery who died of intractable postoperative hypotension. This was followed by a similar report in 1953 by Lewis et al.⁷ The lack of hemodynamic and electrocardiographic monitoring and the failure to mea-

sure corticosteroid levels in both studies make it unclear whether the patients died of an Addisonian crisis. Nevertheless, since the publication of these 2 case reports, stress doses of corticosteroids have become a regular part of perioperative management in patients undergoing long-term corticosteroid therapy. It was presumed that, because of the atrophy of the adrenal gland and suppression of the HPA axis, not enough endogenous glucocorticoids would be produced to meet the demands of the operative stress and that signs and symptoms of adrenocortical insufficiency would develop in the absence of supplemental doses of corticosteroids. A clinical consensus has therefore developed that patients who are exposed to major physical stress such as an operation need high supplemental doses of corticosteroids during the stressful period.²⁻⁵

Because the use of stress doses of corticosteroids has become routine in the perioperative management of patients receiving long-term corticosteroid therapy, the true incidence of perioperative adrenal crisis is difficult to determine. However, Kehlet⁸ and Salem et al⁵ have reviewed the world literature and reported only 3 cases in which death or hypotension could be attributed to perioperative adrenal crisis in patients receiving glucocorticoids. It is therefore possible that many patients needlessly receive supplemental perioperative corticosteroid therapy. The goal of this study was to perform a critical review of the published literature to determine the optimal approach to corticosteroid replacement in the perioperative period.

METHODS

IDENTIFICATION OF TRIALS

Our aim was to identify all relevant clinical trials that studied the role of perioperative corticosteroids and adrenal crisis in patients taking long-term therapeutic doses of corticosteroids. We sought to identify randomized studies that compared stress doses of corticosteroids with placebo and prospective cohort studies that followed up patients after surgery in which perioperative stress doses of corticosteroids were not administered. We used a multimethod approach to identify relevant studies for this review. Both of us independently searched the National Library of Medicine's MEDLINE database for relevant studies in any language published from January 1, 1966, through July 31, 2007, using the medical subject headings and keywords *perioperative care* [explode] or *perioperative or surgery* [explode] and *adrenal cortex hormones* [explode] or *corticosteroids*. We limited the search to studies involving humans and adults. In addition, we searched EMBASE and the Cochrane Database of Systematic Reviews. Bibliographies of all selected articles and review articles that included information on perioperative corticosteroid use were also reviewed for other relevant articles. This search strategy was performed iteratively, until no new potential citations were found on review of the reference lists of retrieved articles.

STUDY SELECTION AND DATA EXTRACTION

Both investigators independently identified relevant studies. Disagreements were resolved by consensus. Extracted data included study design, the number of patients and surgical procedures performed, previous corticosteroid dosage and duration

of treatment, results of HPA axis testing, corticosteroid regimen used, and hemodynamic consequence of the corticosteroid regimen. Because the population characteristics and outcome variables of the studies were not conducive to quantitative analysis (meta-analysis), only a descriptive analysis was performed.⁹

RESULTS

The initial search strategy generated 296 citations; of these, 274 were not relevant and an additional 15 were excluded owing to study design (ie, retrospective, did not report outcome variable of interest, or duplicate publication). An additional 2 studies were identified by reviewing the bibliographies of the identified studies and review papers. Nine studies therefore met our inclusion criteria (**Table**).¹⁰⁻¹⁹ There were no disagreements between the reviewers with regard to inclusion of studies or data variables. The 9 studies enrolled a total of 315 patients who underwent 389 surgical procedures. Two of the studies were prospective, double-blind, randomized, placebo-controlled studies in which patients received perioperative stress doses of corticosteroids or placebo together with their usual maintenance dose of corticosteroid.^{17,18} In 2 studies, corticosteroid therapy was stopped before surgery (18 and 36 hours before surgery),^{10,11} whereas in an additional 5 studies patients were followed up after receiving only their usual daily maintenance dose of corticosteroid.¹²⁻¹⁶ Stress doses of corticosteroids were not administered in these 7 studies. The results of these studies are summarized in the Table and discussed herein.

Glowniak and Loriaux¹⁷ randomized 17 corticosteroid-dependent patients with secondary adrenal insufficiency (determined by results of cosyntropin testing) who were undergoing a major surgical procedure to receive stress doses of corticosteroids or their usual daily dose combined with a placebo. There was no major difference between these groups in perioperative or postoperative blood pressure, with a single patient in each group having volume-responsive hypotension. Thomason and colleagues¹⁸ performed a double-blind crossover study in 20 organ transplant recipients undergoing gingivectomy under local anesthesia. Each patient required 2 gingivectomies and thus acted as his or her own placebo control, receiving 100 mg of hydrocortisone or placebo in addition to the patient's usual daily dose of glucocorticoid. There was no significant difference in blood pressure between the groups, and no patient experienced symptoms suggestive of adrenal insufficiency.

In 1968, Jasani and colleagues¹⁰ reported the results of their now classic study. The authors studied 41 patients with rheumatoid arthritis who underwent anterior synovectomy. Twenty-one of these patients were receiving oral corticosteroid therapy; the remaining 20 patients served as controls. Oral corticosteroid therapy was discontinued 18 hours before surgery in all patients except one in whom it was discontinued 48 hours before surgery. The integrity of the HPA axis was assessed preoperatively with cosyntropin, vasopressin, insulin hypoglycemia, and metyrapone tests, and plasma 11-hydroxycorticosteroid levels were measured preopera-

Table. Studies Investigating the Use of Perioperative Corticosteroids

Source	No. of Patients	Design	Patient Description	Previous Corticosteroid Treatment ^a	Surgical Procedure	Corticosteroid Treatment	Abnormal Corticotropin Level, No. (%)	Hemodynamic Profile
Jasani et al, ¹⁰ 1968	21/20 ^b	P CC	RA	7 mg/3 y	Synovectomy	Stopped 18 h before surgery; restarted 6 h after surgery	9 (43)	1 Hypotensive collapse ^c
Kehlet and Binder, ¹¹ 1973	104	P cohort	Various	NR	74 Major and 30 minor surgical procedures	Stopped 36 h before surgery; restarted 72/24 h after major/minor surgery	31 (64) ^d	1 Hypotensive collapse ^e
Shapiro et al, ¹² 1990	13	P cohort	Renal allograft	10 mg/1 y	Nephrectomy	Usual daily dose	6 (46)	No unexplained hypotension
Bromberg et al, ¹³ 1991	40/62 ^f	P cohort	Renal allograft	5-10 mg/>3 mo	Various	Usual daily dose	25 (62)	No unexplained hypotension
Bromberg et al, ¹⁴ 1995	52/58 ^f	P cohort	Renal allograft	5-15 mg/>2 mo	Various	Usual daily dose	ND	No unexplained hypotension
Friedman et al, ¹⁵ 1995	28/35 ^f	P cohort	Renal allograft, RA	10 mg/7 y	Orthopedic	Usual daily dose	ND	No unexplained hypotension
Mathis et al, ¹⁶ 2004	20/38 ^b	R CC	Renal allograft	16 mg/2.8 mo	Lymphocele drainage	Usual daily dose	ND	No unexplained hypotension
Glowniak and Loriaux, ¹⁷ 1997	17/18 ^f	RCT blind	Various	12 mg/2 y (corticosteroid) 16 mg/5 y (placebo)	Various	Usual daily dose with placebo or hydrocortisone, 100 mg, then 25 mg	17 (100) ^g	No difference between groups
Thomason et al, ¹⁸ 1999	20/40 ^f	RCT double-blind crossover	Organ transplant	8 mg/3 y	Gingival, local anesthesia	Usual daily dose placebo or hydrocortisone 100 mg	ND	No difference between groups

Abbreviations: CC, case-control; ND, not determined; NR, not reported; P, prospective; R, retrospective; RA, rheumatoid arthritis; RCT, randomized controlled trial.

^aReported as mean daily dose of prednisone/duration.

^bIndicates number of treatment/control patients.

^cGlucocorticoid therapy was stopped 48 hours before surgery in the patients with hypotensive collapse.

^dIn a subgroup of 48 patients.¹⁹

^eThe patient who experienced hypotensive collapse had known HPA axis failure.

^fIndicates number of patients/surgical procedures.

^gIndicates enrollment criteria.

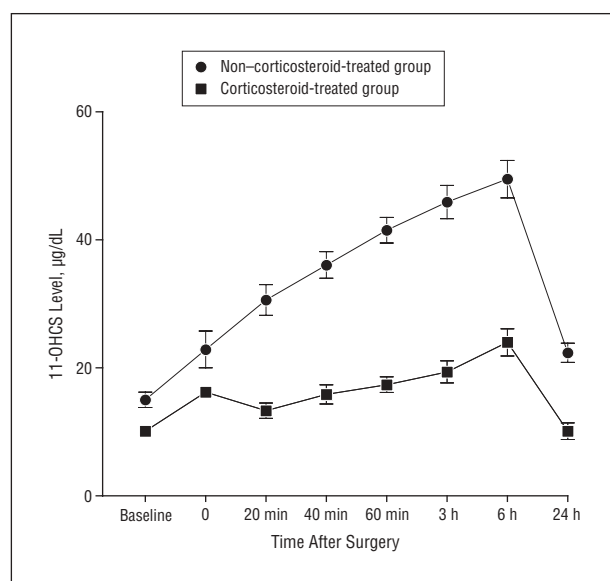


Figure. Plasma 11-hydroxycorticosteroid (11-OHCS) response to surgery in non-corticosteroid- and corticosteroid-treated patients with rheumatoid arthritis. Data from Jasani et al.¹⁰

tively, intraoperatively, and postoperatively. Five of the 21 corticosteroid-treated patients had a normal response to all 4 tests of HPA function. Although the corticosteroid levels increased with the stress of surgery in

both groups, the levels were significantly lower in the corticosteroid-treated patients compared with the controls (**Figure**). In the corticosteroid-treated patients, the corticosteroid levels were lowest in those with an abnormal cosyntropin test result, followed by those with an abnormal response to 1 of the other HPA stimulatory tests. The corticosteroid levels were higher in the corticosteroid-treated patients with a normal response to all 4 tests of HPA function than the other 2 groups; however, the corticosteroid levels were lower than in the controls. Although preoperative systolic blood pressure was slightly (although statistically) lower in the corticosteroid group, there was no difference between the blood pressure profiles during the intraoperative and postoperative measurements. One patient developed intraoperative hypotension that responded rapidly to intravenous hydrocortisone therapy and volume resuscitation. Corticosteroid therapy was stopped 48 hours before surgery in that patient.

In 1973, Kehlet and Binder¹¹ reported the results of a study in which 104 glucocorticoid-treated patients underwent surgery without supplemental stress doses of glucocorticoids. In that study, glucocorticoid therapy was stopped 36 hours before surgery and readministered 24 hours after minor surgery and 72 hours after major surgery. Plasma corticosteroid levels were measured during the 24-hour postoperative period. In the patients undergoing major surgery, the mean corticosteroid value 1 hour after skin inci-

sion increased significantly from baseline. However, the response was impaired (compared with the control group) in 39 patients undergoing major surgery (53%). Both the duration and dose of glucocorticoid treatment before surgery were associated with the degree of impairment of the corticosteroid response. Only 1 patient had a low serum cortisol level (total serum cortisol level, $<10 \mu\text{g/dL}$ [to convert to nanomoles per liter, multiply by 27.588]) 4 hours after skin incision. There were 7 instances of hypotension, all of which resolved spontaneously or in response to fluid administration. None of the patients undergoing major surgery developed shock, and the hypotension was of short duration (<20 minutes in all patients). There was no relationship between the postoperative corticosteroid level and the development of hypotension. Nine of the patients undergoing minor surgery (30%) demonstrated an abnormal corticosteroid response. One patient undergoing minor surgery developed unexplained intraoperative hypotension. That patient was known to have severe adrenocortical failure and responded to 50 mg of hydrocortisone and fluid resuscitation.

Shapiro and colleagues¹² performed allograft nephrectomies in 13 patients receiving immunosuppressive doses of corticosteroids. The patients continued to receive their maintenance dose of prednisone during the perioperative period. Despite 6 (46%) of the patients having evidence of adrenal suppression on results of cosyntropin testing, none developed signs or symptoms of adrenal insufficiency. Similarly, Bromberg and colleagues¹³ studied 40 renal allograft recipients who were admitted to the hospital with significant physiologic stress and required various surgical procedures. The patients received only their baseline dose of prednisone. Despite the fact that 25 patients (62%) had evidence of adrenal dysfunction on results of cosyntropin testing, the 24-hour urinary level of free cortisol was elevated or in the high reference range in most of the patients; only 1 patient had a low level. None of the patients developed clinical evidence of adrenal insufficiency. In a follow-up study,¹⁴ these authors studied 52 recipients of renal allografts who underwent 58 operative procedures. No patient received stress doses of corticosteroids but only their baseline immunosuppressive doses of glucocorticoids. No patient developed clinical signs of adrenal dysfunction, and all patients had increased urinary excretion of free cortisol compared with baseline unstressed levels.

Friedman and colleagues¹⁵ performed a prospective study in 28 patients receiving immunosuppressive doses of glucocorticoids who were undergoing major orthopedic operations. In their study, the patients did not receive stress doses of corticosteroids; they were given only their usual daily dose of glucocorticoid. No patient developed clinical evidence of adrenocortical insufficiency during the hospital stay. Despite receiving adrenally suppressive dosages of glucocorticoids before surgery, most patients (20 [71%]) increased production of endogenous corticosteroid (urinary level of free cortisol) in response to the operative stress. Mathis and colleagues¹⁶ compared the outcomes of renal- or pancreas/kidney-transplant recipients undergoing surgical lymphocele drainage who received ($n=20$) or did not receive ($n=38$) perioperative stress doses of corticoste-

roids. There was no difference in morbidity between the 2 groups, with none of the patients developing clinical evidence of adrenal insufficiency.

COMMENT

The 2 randomized placebo-controlled studies included in this review did not detect a difference in the hemodynamic profile of patients treated with stress doses of corticosteroids compared with patients treated with their usual dose of corticosteroid alone. These results are supported by the 5 cohort studies¹²⁻¹⁶ in which patients received their usual daily dose of corticosteroid without the addition of stress doses of corticosteroids; none of the patients in those 5 studies developed an adrenal crisis. One patient in each of the studies by Jasani et al¹⁰ and Kehlet and Binder¹¹ developed a possible adrenal crisis that responded rapidly to hydrocortisone treatment; in those patients, corticosteroid therapy was stopped 36 and 48 hours before surgery. These data suggest that, in patients receiving long-term corticosteroid therapy, stress doses of corticosteroids are not required; however, the patients should continue to receive their usual daily dose of corticosteroid. Furthermore, although these patients are likely to have an abnormal cosyntropin test result, they are able to increase production of endogenous glucocorticoids. This suggests that the demands of physiologic stress are met by a combination of increased endogenous adrenal function plus exogenous baseline doses of glucocorticoids. Supraphysiologic or stress-dose corticosteroid therapy is therefore not required.

These data are supported by an experimental study reported by Udelsman and colleagues²⁰ in which adrenalectomized monkeys undergoing open cholecystectomy were randomized to receive subphysiologic (one-tenth the normal cortisol production rate), physiologic, or supraphysiologic (10 times the normal cortisol production rate) perioperative doses of hydrocortisone. The group receiving the subphysiologic treatment had reduced blood pressure, cardiac index, and systemic vascular resistance and higher mortality when compared with the other 2 treatment groups and the control group undergoing sham operation. In contrast, the group receiving physiologic treatment was indistinguishable from the group receiving supraphysiologic treatment and the control group.

Although the studies included in this analysis are limited by their small sample size, the data suggest that, in patients receiving long-term adrenally suppressive doses of glucocorticoids, the combination of the patient's baseline exogenous corticosteroid (usual daily dose) plus endogenous steroid production is able to meet the demands of the physiologic stress of surgery. Biochemical testing of the HPA axis in patients receiving glucocorticoid therapy may reveal adrenal insufficiency; however, these tests do not predict the clinical outcome and are too sensitive to guide decisions regarding treatment.^{15,17,18} This suggests that routine perioperative stress doses of corticosteroids are not required in addition to the patients' usual daily corticosteroid dose. However, the anesthesiologist, surgeon, and intensivist must be

aware that the patient was receiving suppressive doses of corticosteroids, necessitating close perioperative hemodynamic monitoring and the use of stress doses of hydrocortisone in patients with volume-refractory hypotension. (A serum cortisol level should be measured in these patients before initiating treatment.)

These recommendations do not apply to patients who receive physiologic replacement doses of corticosteroids because of primary dysfunction of the HPA axis (eg, patients with primary adrenal failure due to Addison disease, with congenital adrenal hyperplasia, or with secondary adrenal insufficiency due to hypopituitarism). It is likely that these patients are unable to increase endogenous cortisol production in the face of stress. These patients require adjustment of their glucocorticoid dose during surgical stress under all circumstances. The reference cortisol secretory rate in response to general anesthesia and major surgery is estimated to range from 75 to 150 mg/d.^{5,21} The cortisol secretory rate in response to minor procedures is approximately 50 mg/d. Therefore, patients receiving physiologic replacement doses of glucocorticoids and undergoing surgery should receive 50 mg of hydrocortisone intraoperatively. This dose should be continued for 48 to 72 hours postoperatively at an interval of 8 hours in patients undergoing major surgery.

Our study lacks statistical power because of the small sample size (total of 315 patients) and the apparent low incidence of adrenal crisis in this group of patients. Additional studies are therefore warranted. In addition, it could be argued that clinicians should have a low threshold for treating such patients with perioperative stress doses of corticosteroids (in a dosage regimen as outlined herein) because of the lack of adverse effects of such a strategy. This may be particularly relevant in patients who are unable to take their medications orally or when etomidate is used as the induction agent. Etomidate inhibits the 11 β -hydroxylase enzyme that converts 11 β -deoxycortisol into cortisol and predictably reduces cortisol synthesis for up to 48 hours after a single intubating dose of this hypnotic agent.²²⁻²⁴ This latter caveat may be particularly important because the use of this agent was not reported in any of the studies included in our analysis.

In conclusion, patients receiving therapeutic doses of corticosteroids who undergo a surgical procedure do not routinely require stress doses of corticosteroids so long as they continue to receive their usual daily dose of corticosteroid. Adrenal function testing is not required in these patients because the test is overly sensitive and does not predict which patients will develop an adrenal crisis. However, patients receiving physiologic replacement doses of corticosteroids owing to primary disease of the HPA axis require supplemental doses of corticosteroids in the perioperative period.

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