Perioperative Stress-Dose Steroids

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Clin Colon Rectal Surg 2013;26:163–167.

Abstract

Supraphysiologic corticosteroid doses have routinely been considered the perioperative standard of care over the past six decades for patients on long-term steroid therapy. However, the accumulation of data over this period is beginning to suggest that such a practice may not be necessary. The majority of these studies are retrospective reviews or small prospective cohorts, but there are two small prospective, randomized placebo-controlled trials, one prospective primate trial, and several systematic reviews addressing the issue. Based on this developing evidence, patients on long-term exogenous steroids do not require high-dose perioperative corticosteroids and should instead remain on their baseline maintenance dose, with the understanding that secondary adrenal insufficiency should be considered for unexplained perioperative hypotension in these patients.

Keywords

- stress-dose steroids
- adrenal insufficiency
- corticosteroids
- perioperative steroids

Objectives: On completion of this article, the reader should have an understanding of the current perioperative management of patients on long-term steroid therapy and of the evidence guiding these recommendations.

Historical Context

In 1949, the glucocorticoid cortisone was developed, giving physicians the ability to effectively treat adrenal insufficiency.¹ That same year Hench and colleagues discovered that it was possible to use oral glucocorticoids for the treatment of chronic rheumatoid arthritis, marking the beginning of the use of these agents for immunosuppression and numerous other chronic inflammatory conditions.² Shortly thereafter, a single case report in 1952 by Fraser et al described a 34-year-old man with rheumatoid arthritis undergoing hip arthroplasty who developed hemodynamic collapse immediately following his operation. He had been treated with cortisone for 8 months with dosing at 25 mg twice daily for the 2 months prior to surgery; this had been discontinued 2 days before the operation. Autopsy showed bilateral adrenal atrophy, leading the authors to suggest that his death could be attributed to acute adrenal insufficiency.³ A case presented by Lewis et al in 1953 described a 20-year-old woman with rheumatoid arthritis undergoing knee surgery, who had

developed hemodynamic instability progressing to death just 5 hours after surgery. Similar to the other case, she had been on cortisone for 5 months preoperatively, which had been discontinued the day prior to surgery. Autopsy showed bilateral adrenal atrophy and hemorrhage.⁴ This case led to the recommendation that patients on chronic oral steroids should receive perioperative supraphysiologic “stress-dose” corticosteroids (up to four times baseline dose) to avoid the precipitation of adrenal crisis.^{2,4}

Although it is well known that both medical and surgical stress cause increases in cortisol production, the response and cortisol requirements of patients with hypothalamic-pituitary-adrenal (HPA) axis suppression due to exogenous steroid administration during stress are poorly understood.¹ There is a lack of consensus regarding perioperative steroid dosing for these patients. Furthermore, there is little historical data available regarding the true incidence of perioperative adrenal insufficiency. The majority of studies base the definition of adrenal insufficiency on hypotension and non-specific symptoms (tachycardia, fever, lethargy, arthralgias, myalgias, nausea, emesis, mental status changes), without laboratory evaluation of the HPA axis. A review in 1976 by Kehlet found that only 3 of 57 cases of hypotension suspected to be due to adrenal insufficiency could be confirmed biochemically.⁵

Issue Theme Perioperative Management; Guest Editor, Sharon L. Stein, MD, FACS

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Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0033-1351132>.
ISSN 1531-0043.

Despite the lack of supportive evidence in the past 60 years, supraphysiologic corticosteroid doses have been routinely used in the perioperative period for patients on long-term steroid therapy. However, numerous small studies and reviews are beginning to question this practice. Given that colorectal surgeons are commonly faced with the challenge of operating on patients with inflammatory bowel disease (IBD) who are on chronic steroids, as well as patients on chronic steroids for a litany of medical issues, an understanding of the history and debate surrounding perioperative stress-dose steroids is critical in caring for this population.

Pathophysiology

The adrenal glands are responsible for producing a variety of regulatory steroid hormones and catecholamines.⁶ The adrenal cortex's zona fasciculata produces glucocorticoids, mainly cortisol, and is stimulated by adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. ACTH is stimulated by corticotrophin-releasing hormone (CRH), which is secreted by the hypothalamus. Cortisol acts in cell cytoplasm and has a role in metabolism, homeostasis, wound healing, cardiovascular system maintenance, catecholamine production, and self-regulation via a negative feedback loop to decrease secretion of CRH and ACTH.¹ The adrenal gland produces an estimated 5.7 mg/m² of cortisol daily (with levels peaking at 4–8 AM), which can increase 5- to 10-fold during times of stress.^{1,7} Prolonged elevation of cortisol either endogenously or exogenously can lead to side effects such as hyperglycemia, immunosuppression, hypertension, delayed wound healing, volume overload, and psychosis.¹

Primary adrenal insufficiency occurs with destruction of more than 90% of the adrenal glands by infection, inflammation, tumor, or hemorrhage, and results in decreased glucocorticoid and mineralocorticoid production.¹ Secondary adrenal insufficiency is far more common and is most often caused by prolonged administration of exogenous steroids. The resulting suppression of ACTH and CRH secretion causes a decrease in endogenous glucocorticoid production and eventual adrenal atrophy.⁶ Patients with a normal HPA axis who are exposed to increased levels of stress will secrete increased amounts of cortisol, while patients exposed to chronic exogenous steroids exhibit blunted responses and have traditionally been considered at risk for adrenal crisis during these periods.⁸ The original recommendation of 200 to 300 mg of hydrocortisone as a supraphysiologic dose stemmed from the idea that this would be the amount of cortisol produced by a maximally stimulated adrenal gland.⁷ There is widespread disagreement about the amount, duration, and total exposure of exogenous steroids required to cause HPA-axis dysfunction and how long the glands take to fully recover function after discontinuation of therapy.¹

Existing Evidence

Over the past five decades, several studies have evaluated the utility of giving supraphysiologic corticosteroids during the perioperative period to patients on chronic steroids. The

evidence is lacking, however, because the majority of these studies are retrospective reviews or small prospective cohorts.^{9–18} There are currently two small prospective, randomized placebo-controlled trials and one prospective primate trial addressing the subject.^{19–21}

Although many of the studies on supraphysiologic perioperative steroids have their limitations, following their results over time allows us to trace the current understanding, dilemmas, and evolution of this topic. The earliest studies examined adrenal insufficiency in patients whose steroids were stopped preoperatively. In 1962, Solem and Lund described a group of 30 patients who were followed after the discontinuation of their chronic steroids 4 weeks prior to surgery. They noted that no corticosteroid coverage was required in the perioperative period to prevent hypotension.^{8,9} Six years later, Jasini et al studied a group of 41 patients with rheumatoid arthritis undergoing anterior synovectomy. They looked at 21 patients who were taking chronic oral steroids stopped 18 hours prior to surgery, compared with 20 control patients not on steroids. They followed several biochemical markers of the HPA axis, including plasma 11-hydroxycorticosteroid levels. Although both groups showed an increase in 11-hydroxycorticosteroid in response to surgical stress, the steroid group had overall lower levels than the control group. However, this did not manifest clinically. Interestingly, the one patient off steroids for 48 hours preoperatively developed the only noted episode of intraoperative hypotension, which was managed successfully with fluid resuscitation and hydrocortisone.^{10,22}

In 1973, Kehlet and Binder prospectively followed 73 patients receiving long-term oral prednisone (5–80 mg/d) that was discontinued 36 hours prior to surgery and resumed 72 hours postoperatively. They measured plasma cortisol levels at multiple time points and followed the patients clinically. Seven of 18 cases of perioperative hypotension could not be explained by sepsis or bleeding, but only three of these seven patients had low cortisol levels recorded and were considered as having true adrenal insufficiency.^{7,11}

A larger retrospective study in 1981 by Knudsen et al examined 250 patients with inflammatory bowel disease taking an average 40 mg of prednisone daily. One group received supraphysiologic steroids in the perioperative period and the other group did not. Hypotension occurred in 22% of the group receiving steroids versus 9% in the nonsteroid group, but only 2 of 18 cases of hypotension were attributed to adrenal insufficiency.^{7,8,12} The same year Lloyd prospectively followed 61 patients on long-term corticosteroid therapy for rheumatoid arthritis undergoing various orthopedic procedures. He found no statistical differences in supplemental steroid requirement between the group who received 100 mg of hydrocortisone preoperatively and the other group who did not receive perioperative steroids.¹³ His study highlighted the idea that patients could receive “rescue” doses of steroids when adrenal insufficiency was known to be in the differential for perioperative hypotension.⁸

During the 1980s, researchers began exploring the idea that patients may not need to be taken off of their baseline

steroid doses preoperatively and that perhaps supraphysiologic corticosteroid doses did not have to be as high as initially hypothesized. In 1981, Symreng et al followed a prospective cohort of 14 patients who underwent preoperative ACTH stimulation tests. Patients with a normal test did not receive additional perioperative steroids, while those with an abnormal test were supplemented with 25 mg of hydrocortisone at incision, followed by 100 mg hydrocortisone over the first 24 hours. Neither group demonstrated clinical evidence of adrenal insufficiency, suggesting that lower stress doses may be adequate.⁸

In 1986, Udelsman et al developed a primate model to more closely examine adrenal insufficiency and the dosing of perioperative steroids. Thirty cynomolgus monkeys were divided into four groups. Three quarters of the monkeys underwent bilateral adrenalectomy and one quarter underwent a sham adrenalectomy. In the 4 months of recovery time, the adrenalectomized monkeys received glucocorticoid and mineralocorticoid replacement and the sham monkeys received normal saline. At the end of this period, for 4 days prior to cholecystectomy, one group received subphysiologic hydrocortisone, a second group received physiologic hydrocortisone, a third group received supraphysiologic hydrocortisone, and the fourth sham group received no steroids. Following cholecystectomy, the monkeys' hemodynamics and clinical outcomes were monitored closely. The group receiving subphysiologic steroid replacement had significantly higher mortality and cardiovascular instability. Both the physiologic and supraphysiologic groups had similar outcomes with no differences in wound healing, suggesting that while physiologic doses were adequate and supraphysiologic doses were not particularly harmful, subphysiologic doses had significant negative clinical consequences.²¹

With this information, subsequent studies explored leaving patients on perioperative doses equivalent to their baseline exogenous steroid requirements. Shapiro et al noted that 6 of 13 patients on corticosteroids following allograft nephrectomy showed evidence of HPA axis suppression on an ACTH stimulation test, but had no clinical evidence of adrenal suppression when continued on their maintenance prednisone perioperatively.^{15,22} Similarly, Bromberg et al examined a prospective case series of 40 renal transplant patients on long-term steroids and immunosuppressants undergoing additional operations, and found that 63% had abnormal ACTH stimulation tests, but 97% had normal or increased urinary cortisol levels sufficient for stress. All were maintained on their baseline steroid dosing without clinical evidence of adrenal insufficiency.^{2,16} In 1995, Friedman et al followed 28 patients on chronic prednisone (1–20 mg/d) who were kept on only their equivalent baseline dose while undergoing an orthopedic procedure. There was no clinical evidence of adrenal insufficiency in this prospective series. Urinary cortisol measurements perioperatively and several weeks later were not significantly different or predictive of clinical outcomes.¹⁷

By the late 1990s, there was a wealth of observational data collected regarding perioperative supraphysiologic steroid dosing, but no randomized clinical trials. In 1997, Glowniak

and Loriaux performed a randomized double-blinded trial on 18 men undergoing surgery who had received at least 2 months of daily prednisone. An ACTH stimulation test showing inadequate response was necessary for inclusion. All patients received their baseline prednisone dose. In addition, one group of six patients received 100 mg of hydrocortisone before surgery, then 25 mg every 6 hours for 2 days, and 25 mg every 12 hours for one day. The other group of 12 patients received normal saline in the same dosing schedule. There was no statistical difference in hypotension and heart rate before, during, or after the procedure. The authors asserted that supplemental stress-dose steroids do not prevent perioperative hypotension, although their study may not have been powered to detect a statistical difference.¹⁹

A second randomized double-blind crossover study was performed in 1999 by Thomason et al. They examined renal and cardiac patients on prednisone (5–10 mg/d) and other immunosuppressive medications requiring gingival surgery in at least 2-month quadrants. Twenty patients were included and randomly received either 100 mg hydrocortisone or placebo on their first surgery and the opposite on their second surgery. A postprocedure ACTH level was drawn and blood pressure was monitored closely. The authors found no clinical manifestation of adrenal insufficiency despite some patients exhibiting HPA suppression based on ACTH levels, and concluded that stress-dose steroids were not required.²⁰

Most recently, Zaghiran et al studied patients with inflammatory bowel disease. In their retrospective review of 38 patients who were not on steroids at the time of major colorectal procedure, but had taken at least 5 mg prednisone for greater than 1 week in the past year, they compared a group receiving supraphysiologic hydrocortisone (100 mg every 8 h for 24 h, tapered to 20 mg daily over 3 d) with a group not receiving perioperative steroids. They noted an increase in heart rate in the steroid group, but otherwise no difference in hemodynamic stability or need for rescue steroids. They concluded that IBD patients could be safely managed without stress-dose steroids.²³ Zaghiran's group went on to study 32 IBD patients undergoing major colorectal surgery. Patients on steroids at the time of surgery were given intravenous (IV) hydrocortisone (one-third equivalence of baseline at incision tapering to one-sixth equivalence of baseline every 12 hours on postoperative day 3) and patients not currently on steroids (but with a history of steroid use in the last year) were given no extra therapy. Hypotensive events were similar between groups and the authors suggested that their new, low-dose perioperative regimen could be appropriate for this population.²⁴

Several systematic reviews, including a Cochrane Review, have summarized the available evidence regarding perioperative supraphysiologic corticosteroid administration over the past 20 years; however, recommendations have not remained consistent during this period.^{1,2,8,22,25} They do agree that the doses in the range of 200 to 300 mg of hydrocortisone once recommended are probably too high and put patients at risk for steroid-induced side

effects. In 1994, Salem et al felt that patients receiving greater than 20 to 30 mg of prednisone per day were at a reasonable risk of HPA-axis suppression and should have biochemical testing of the HPA axis if possible. If this was not available or there was clinical evidence of adrenal insufficiency, then perioperative steroids should be given and adjusted based on the estimated surgical stress. Patients on chronic steroids who undergo minor procedures (hernia repair, colonoscopy) should get a single dose of 25 mg hydrocortisone, moderate procedures (open cholecystectomy, colon resection, hysterectomy, joint replacement) should get 50 to 75 mg hydrocortisone for 1 to 2 days, and major procedures (abdominoperineal resection, pancreaticoduodenectomy) should get 100 to 150 mg hydrocortisone for 2 to 3 days.² These recommendations remained similar in a 2001 *Journal of the American Medical Association* review by Coursin and Wood, which stated that patients should get their baseline oral steroid in IV form and a stress dose based on the surgical procedure. Dosing was identical to Salem et al's recommendation except Coursin and Wood recommended a steroid taper on postoperative day 1 and 2 for both moderate and major procedures.¹

A 2008 systemic review by Marik and Varon included nine studies and 315 patients. Meta-analysis was not possible due to varied outcome measures. Their conclusion reflects a changing paradigm, emphasizing that many biochemical tests are too sensitive and do not translate into clinical outcomes. For most patients, continuing the baseline steroid dose is appropriate and recommended—with the awareness that stress-dose steroids could be administered in patients with hypotension unresponsive to standard measures.²² Yong et al echo this change in their Cochrane Review, which includes only 37 patients from the randomized controlled trials. These trials suggest that supraphysiologic corticosteroid dosing is not necessary preoperatively to prevent adrenal insufficiency, but that current evidence is not adequate to fully support or refute this claim.²⁵

Conclusion

In the 60 years since Fraser reported the first case of perioperative adrenal crisis in a patient on exogenous steroids, very little progress has been made regarding recommendations for these patients. The numerous retrospective or small-scale studies and the inherent low incidence of perioperative adrenal insufficiency highlight the need for a large, prospective, randomized controlled trial. In specialties like colorectal surgery that commonly treat patients on long-term steroids, adrenal insufficiency should remain on the differential diagnosis of perioperative hypotension, but it is far less common than hemorrhage or sepsis. Modern biochemical tests have the ability to detect changes in cortisol and ACTH levels, but these are not always proven to be clinically significant. Based on the existing evidence, it is recommended that patients on long-term exogenous steroids do not require the high-dose corticosteroids that were once the standard of care. Rather, patients should remain on their baseline maintenance doses

throughout the perioperative period and be treated for hypotension that is otherwise unresponsive or unexplained with a rescue dose of steroids.

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