

Stress Dose Steroids: Myths and Perioperative Medicine

Literature Review by Sina Moshiri

Introduction

- Many patients presenting for surgery receive regular doses of glucocorticoids for treatment of systemic autoimmune inflammatory disease, asthma and chronic pulmonary disease, and post organ transplantation
- Traditionally, supplemental dosing of glucocorticoids prior to surgery was thought to be necessary in these patients to avoid hypotension and shock
- Alternative strategies were rarely considered, and patients still often receive preoperative steroids despite the known infectious, metabolic and wound healing risks associated with glucocorticoids
- Recommendations for perioperative glucocorticoid management have remained unchallenged despite the relative frequency with which many patients use glucocorticoids, and the little evidence supporting this practice
- Rationale behind this practice was based on the positive feedback inhibition governing the hypothalamic-pituitary-adrenal (HPA) axis. It was thought that long-term, iatrogenic glucocorticoid administration would result in suppression of the HPA axis and increase risk of adrenal crisis in response to surgical stress.
- This paper seeks to review the perioperative mechanism and use of glucocorticoids, and review the literature and recommendations on which these practices are based.

Adrenal Physiology

- The body consists of two adrenal glands situated on top of the kidneys. These glands help maintain homeostasis through production of two hormones, cortisol (glucocorticoids) and aldosterone (mineralocorticoid).
- Adrenal glands are involved in electrolyte and fluid balance, which is regulated by a feedback mechanism. Release of corticotropin releasing hormone (CRH) from hypothalamus, stimulates the release of adrenocorticotrophic (ACTH) from the pituitary gland. ACTH triggers the production of cortisol by the adrenal glands.
- Cortisol is released in response to stress and low blood sugar, and has various metabolic effects on the body.
- At normal conditions the body produces 10-12 mg cortisol per day. Serum levels consist of 18-20 ug/dl, 30-45 ug/dl, and as high as 260 ug/dl in mildly, moderately and life threatening levels of stress, respectively. Cortisol levels normalize within 24-48 hours of the stressful event.
- Glucocorticoid secretion increases in proportion to the degree of stress. Surgery is a potent stressor that triggers the HPA axis by raising ACTH levels. Levels of cortisol may remain elevated for up to 24-48 hours, and may increase by 5-10 times versus a baseline of 20-30 mg/day of hydrocortisone (5-7 mg/day of prednisone).
- Adrenal insufficiency (AI) occurs due to adrenal gland dysfunction or destruction, resulting in inadequate cortisol needed to maintain homeostasis
- Primary AI (Addison's disease) results from destruction of adrenal cortex and may be due to autoimmune disorders (HIV, CMV) tuberculosis, hemorrhage, tumor metastasis and sepsis. In the USA, 80% of primary AI results from autoimmune adrenalitis, and is often related to other autoimmune disorders such as Hashimoto's thyroiditis, Grave's disease, type I diabetes, premature ovarian failure, hypoparathyroidism and testicular failure

- Secondary and tertiary AI result from hypothalamic or pituitary absence or suppression
- Administration of exogenous glucocorticoids suppresses cortisol production through central inhibition of the hypothalamus. Mineralocorticoid production is usually unaffected since its production is regulated by the renin-angiotensin system.
- 5 mg prednisone (20 mg hydrocortisone) for ≥ 2 weeks has been shown to produce measurable changes to the HPA axis, with decreased cortisol release persisting up to a year after the end of glucocorticoid therapy. However the clinical significance of these findings is unclear and it remains to be seen which patients require supplemental dosing.
- The magnitude of adrenal suppression depends on numerous factors, including dose, duration, frequency and route of administration.

Origins and Rationale of Stress Dosing

- First case reporting the surgical risks associated with previous long term glucocorticoid use involved a patient who died due to hypotension during orthopedic surgery (Fraser, 1952). The life threatening sequelae consisting of nausea, vomiting, hypoglycemia, hyponatremia, hyperkalemia, hypotension and shock was termed adrenal crisis.
- The demonstration of adrenal atrophy after autopsy and the severity of the adverse events drove the development of the concept of “stress dosing” – administration of steroids in perioperative and other stressful medical setting
- Systemic review by Marik and Varon examining the use of stress dosing found a lack of strong data and small sample size; only 315 patients comprise the patient base from which this practice is justified
- An RCT by Glowniak and Loriaux found no difference in the intra- and post-operative blood pressure in glucocorticoid dependent patients receiving either a stress dose or a placebo prior to surgery
- Thomason et al. (1999) performed a double-blind crossover study involving 20 organ transplant patients undergoing gingivectomy under local anesthesia. No significant differences in blood pressure and no adverse symptoms were noted in any patients.
- A Cochrane review of RCT examining stress dose steroids for surgical patients with adrenal insufficiency found the current evidence to be limited by a small sample size. The authors concluded the use of supplemental steroid dosing could neither be supported or refuted (Yong et al. 2009).
- The most extensive investigation of adrenal physiology during surgery in glucocorticoid dependent patients involved a cohort study with 41 patients with rheumatoid arthritis undergoing synovectomy of the knee. Half of the patients received oral steroids prior to surgery. All patients discontinued glucocorticoids 18 hours before surgery. HPA axis was thoroughly evaluated prior to, during and after surgery. In all cases, there were small yet clinically insignificant changes in blood pressure during the peri- and postoperative periods. One patient who had stopped glucocorticoids 48 hours prior to surgery developed hypotension during surgery which was managed successfully with hydrocortisone and fluids.

Perioperative Steroid Management

- Based on the available, impactful evidence available the authors continue that traditional practice of supplemental glucocorticoids may result in unnecessary exposure to steroids, leading to hyperglycemia, hypertension, fluid retention and increased risk of infection. In particular, research indicates recent doses of glucocorticoids have the greatest impact on infection risk, with prednisone doses of $>15\text{mg/day}$ identified as a risk factor for prosthetic joint infection.

- A more conservative approach to supplemental glucocorticoid dosing is indicated. The authors' recommendations are summarized below:

Table 1 Recommendations for perioperative steroid therapy in adults

No supplemental steroids	Minor/intermediate intensity surgical procedures Prednisone (or equivalent) ≤ 10 mg daily Every other day steroids Topical steroids
Hydrocortisone 50 mg intraoperatively and q8h after surgery until tolerating po intake when the patient's usual dosage should be restarted.	Major surgical procedures Volume-refractory hypotension Patients requiring physiologic replacement therapy ^a

These recommendations are premised on the assumption that patients will maintain their usual glucocorticoid dosing up until and including the day of surgery

^a Patients with primary adrenal failure (Addison's disease), congenital adrenal hyperplasia, secondary adrenal failure due to hypopituitarism

- Stress dosing steroids due to a presumed adrenal insufficiency is unnecessary. Example in which stress dosing is not required include: 1) patients taking ≤ 10 mg/day of prednisone (or equivalent), 2) patients on alternative-day oral regimens, 3) patients using topical steroids. For these circumstances, the recommendation applies regardless on the type of surgery being performed.
- For all other instances, the recommendations are based on the exposure level, type and magnitude of surgery. When deemed appropriate (usually for large surgical procedures), dosage should be based on secretory rate of cortisol during anesthesia and major surgery. This production may range from 75-150 mg/day and a modest dosing paradigm may involve 50 mg hydrocortisone intraoperative q8h for 48-72 hours. Intravenous administration may be replaced by oral intake as soon as the patient can tolerate it.
- Contraindications to conservative management do exist. Conservative approach should not apply to patients with primary (Addison's disease) adrenal failure, hypopituitarism, congenital adrenal hyperplasia or to glucocorticoid-dependent children.
- Ultimately, the treating physician must remain vigilant and must be ready to react to clinical emergencies with exogenous steroids. Should hypotension or other symptoms of adrenal crisis occur that cannot be attributed to other mechanism such as volume depletion, a supraphysiologic dose of steroids is warranted.

Summary

- Supplemental steroid dosing in the context of surgery is a treatment paradigm that remains unchallenged despite the lack of convincing evidence.
- Spurred primarily by a few case reports and supported by a feasible pathophysiology, this practice has persisted for over 60 years.
- Due to the known risks of exogenous glucocorticoid therapy as well as modern evidence and clinical experience, this practice warrants reconsideration
- In order to establish evidence-based guidelines, additional randomized control trials and cohort studies are necessary to evaluate the risk of peri- and postoperative hemodynamic changes in glucocorticoid dependent patients undergoing surgery
- For now, the prudent practitioner will continue providing supplemental steroid dose for the high risk patients (true adrenal insufficiency, extensive surgical procedure) and will practice a more conservative approach for low risk patients (minor surgery with local anesthesia, patients taking ≤ 10 mg prednisone per day)

References

Mackenzie, C. Ronald, and Susan M. Goodman. "Stress dose steroids: myths and perioperative medicine." *Current rheumatology reports* 18.7 (2016): 47.