Adaptation during surgical stress. A reevaluation of the role of glucocorticoids.

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Research Article

Pharmacologic doses of glucocorticoids are administered to patients with adrenal insufficiency during operative procedures to prevent hemodynamic instability, cardiovascular collapse, and death. Since these supraphysiologic doses might not be necessary and might have adverse effects, we examined the effects of different doses of glucocorticoids on hemodynamic adaptation during surgical stress in adrenalectomized primates. Sham-adrenalectomized placebo-treated animals served as controls. Adrenalectomized monkeys were maintained for 4 mo on physiologic glucocorticoid and mineralocorticoid replacement. The adrenalectomized monkeys were then stratified into three groups receiving, respectively, subphysiological (one-tenth the normal cortisol production rate), physiological, or supraphysiological (10 times the normal cortisol production rate) cortisol (hydrocortisone) treatment. 4 d later a cholecystectomy was performed. The intraoperative hemodynamic and metabolic parameters, perioperative survival rates, and postoperative wound healing were compared. The subphysiologically treated group was hemodynamically unstable before, during, and after surgery and had a significantly higher mortality rate than control. In this group, arterial blood pressure was low, and the cardiac index, systemic vascular resistance index, and left ventricular stroke work index were all reduced, suggesting decreased cardiac contractility and blood vessel tone. In contrast, the physiologically replaced group was indistinguishable from either supraphysiologically treated animals or sham-operated controls. All groups had similar metabolic profiles and normal wound healing. These findings suggest that the permissive actions of physiologic glucocorticoid replacement are both necessary and […]

Adaptation During Surgical Stress

A Reevaluation of the Role of Glucocorticoids

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Abstract

Pharmacologic doses of glucocorticoids are administered to patients with adrenal insufficiency during operative procedures to prevent hemodynamic instability, cardiovascular collapse, and death. Since these supraphysiologic doses might not be necessary and might have adverse effects, we examined the effects of different doses of glucocorticoids on hemodynamic adaptation during surgical stress in adrenalectomized primates. Sham-adrenalectomized placebo-treated animals served as controls. Adrenalectomized monkeys were maintained for 4 mo on physiologic glucocorticoid and mineralocorticoid replacement. The adrenalectomized monkeys were then stratified into three groups receiving, respectively, subphysiological (one-tenth the normal cortisol production rate), physiological, or supraphysiological (10 times the normal cortisol production rate) cortisol (hydrocortisone) treatment. 4 d later a cholecystectomy was performed. The intraoperative hemodynamic and metabolic parameters, perioperative survival rates, and postoperative wound healing were compared. The subphysiologically treated group was hemodynamically unstable before, during, and after surgery and had a significantly higher mortality rate than control. In this group, arterial blood pressure was low, and the cardiac index, systemic vascular resistance index, and left ventricular stroke work index were all reduced, suggesting decreased cardiac contractility and blood vessel tone. In contrast, the physiologically replaced group was indistinguishable from either supraphysiologically treated animals or sham-operated controls. All groups had similar metabolic profiles and normal wound healing. These findings suggest that the permissive actions of physiologic glucocorticoid replacement are both necessary and sufficient for primates to tolerate surgical stress. Supraphysiological glucocorticoid treatment has no apparent advantage during this form of stress in the primate.

Introduction

Since Selye's conception of the general adaptation syndrome, increased adrenal secretion of cortisol has been considered an essential component of the response to stress (1). This notion formed the basis for supplementing stressed adrenal-insufficient patients with high-dose glucocorticoids and has implications that extend widely into clinical practice. In 1971, over 5,000,000 patients in the United States received glucocorticoids at doses sufficient to cause adrenal suppression (2). 10–20% of these patients would, at some time during their course of therapy, be referred for a surgical procedure (3, 4). The current standard of care for these patients includes perioperative high dose glucocorticoids to allegedly prevent hemodynamic instability and cardiovascular collapse.

The role for increased secretion of glucocorticoids during a stress response is unclear (5). It has been suggested that excess glucocorticoids are required to prevent host responses from overreacting to stress (6). Glucocorticoid excess, however, is also associated with undesired immunosuppression, electrolyte imbalance, and delayed wound healing (7–13).

Recent reports have suggested that physiologic cortisol supplementation may be sufficient for patients undergoing major surgical procedures (14–16). Additionally, patients whose glucocorticoid therapy had been discontinued for 3 d–27 mo before surgery tolerated major operations without steroid supplementation (17). These studies challenge the need for excess glucocorticoids in stress. To answer this question in a controlled setting, we developed a primate model and examined the effects of glucocorticoids on the hemodynamic and metabolic adaptation to surgery (18). We studied the ability of adrenalectomized primates to tolerate surgical stress when given subphysiologic, physiologic, or pharmacologic doses of glucocorticoids.

Methods

Protocol. 30 adult male cynomolgus monkeys (*Macaca fasciculata*) were obtained from the National Institutes of Health primate colony, acclimated to their holding facility, and randomly assigned to four groups (7–8 animals/group). Three groups underwent bilateral adrenalectomy and one group had a sham-adrenalectomy. The study design is summarized in Fig. 1. The animals were allowed to recover for 4 mo, during which time the adrenalectomized monkeys received physiologic glucocorticoid and mineralocorticoid replacement and the sham animals received normal saline.

The physiologic cortisol (hydrocortisone) production rate for 32 mg/M^2 per d had been previously determined for the cynomolgus monkey (19). The daily mineralocorticoid (desoxycorticosterone pivalate) dose was 1 mg/d. Injections were given subcutaneously at 9:00 a.m. in an attempt to reproduce a circadian rhythm. Syringes and animals were coded so that the animal caretakers and operating room personnel could not distinguish between groups.

After the recovery period, the adrenalectomized monkeys received a subphysiologic (3.2 mg/M^2 per d; one-tenth time), physiologic (32 mg/M^2/d; 1 time) or supraphysiologic (320 mg/M^2/d; 10 times) dose of hydrocortisone for a period of 4 d. Mineralocorticoid or placebo treatment was continued throughout the experiment in all adrenalectomized and sham-adrenalectomized groups, respectively.

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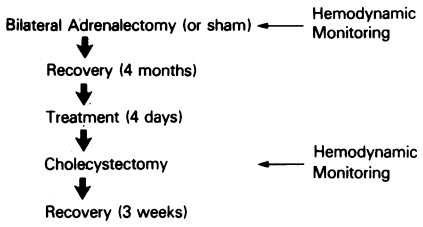

Figure 1. Study design.

After the 4-d treatment period each animal underwent a cholecystectomy. All animals had serial hemodynamic monitoring both during the bilateral (or sham) adrenalectomy and cholecystectomy. Subcutaneous wound chambers were implanted at the completion of cholecystectomy and removed 2 and 3 wk later. Blood samples for hematologic and biochemical tests (see below) were obtained throughout the study period.

Anesthesia. On the morning of surgery, the monkeys received their steroids (or placebo) and were anesthetized with ketamine hydrochloride, 10 mg/kg i.m. (Parke Davis, Morris Plains, NJ). A 20-gauge catheter (Deseret Co., Sandy, UT) was inserted into the superficial saphenous vein and Ringer's lactate was infused at 5 ml/kg per h. Ophthalmic ointment (5% boric acid; Pharmaderm, Melville, NY) was applied to the eyes and penicillin G (44,000 U/kg, Flo-cillin; Bristol Laboratories Div., Bristol-Myers Co., Syracuse, NY) was administered intramuscularly. The surgical areas were prepared as previously described (18).

Sodium thiopental (Pentothal; Abbott, Chicago, IL), 2 ml of a 2.5% solution, was administered and intubation was accomplished with a 4–5 mm cuffed endotracheal tube. Anesthesia was maintained with halothane (0.5%, Halocarbon Products, Corp., Hackensack, NJ) and a 1:1 ratio of nitrous oxide to oxygen at a flow rate of 2 liters/min on a mechanical ventilator (fluidic ventilator; Ohio Medical Products Div., Airco, Inc., Madison, WI). A heating blanket (Blanketrol; Hansen Manufacturing, Cincinnati, OH) was used to maintain a core temperature of 36.5–38.0°C. The intravenous infusions and anesthesia were maintained at constant rates under all circumstances. Additional drugs or fluids were not administered.

Operations. Animals were placed in the supine position, a longitudinal inguinal incision was made, and the femoral vessels were mobilized. The hemodynamic monitoring catheters were inserted under direct vision. After completing the prelaparotomy hemodynamic evaluations, a midline incision was made from the xiphoid process to the symphysis pubis. Bilateral or sham adrenalectomies were performed after mobilization of the right hepatic lobe. In the sham group, the adrenal glands were mobilized and the vascular pedicles identified. The glands, however, were left in situ. The abdomen was closed, the postlaparotomy hemodynamic evaluations were obtained, the vascular catheters were removed, and the femoral vessels were repaired with 7-0 Prolene sutures (Ethicon, Somerville, NJ).

The cholecystectomy was performed 4 mo later through the same midline incision. Dense adhesions, as a result of the first operation, were uniformly encountered. Following abdominal closure, catheter removal, and vascular repair, four separate wound chambers were implanted subcutaneously.

Hemodynamic evaluation. During both operations each monkey underwent pre- and postlaparotomy hemodynamic monitoring with a thermodilution Swan-Ganz catheter (model 93-132-5F; American Edwards Laboratories, Division of American Hospital Supply Corp., Irvine, CA) and an 18-gauge teflon catheter (E-2 cath; Deseret Co.) inserted into the distal pulmonary artery and midabdominal aorta via the common femoral vein or artery, respectively. Swan-Ganz placement was verified by fluoroscopy and pulmonary artery wedge pressure measurements. Serial determinations of cardiac output, pulmonary artery pressure, systemic arterial pressure, right atrial pressure, and pulse rate were determined by three measurements during two separate 5-min observation periods before and after laparotomy. Technical aspects of this primate-hemodynamic model have been previously described in detail (18). All hemodynamic measurements were made during end-exhalation (20) by one investigator.

Hematologic, metabolic, and endocrinologic evaluations. 1 d before surgery and on postoperative day one, blood samples were obtained under ketamine anesthesia (10 mg/kg i.m.) by percutaneous femoral vein puncture. These samples were assayed for serum electrolytes, osmolality, calcium, total protein, albumin, hematocrit, hemoglobin, platelets, and differential white blood cell counts. During surgery blood samples were obtained from the aortic catheter. Differential white blood counts were determined in a blind fashion by a single investigator.

Wound healing evaluation. Stainless steel wire mesh chambers (1.0 × 1.0 × 1.5 cm) were used to analyze tissue inflamation and hydroxyproline deposition as an index of collagen formation during the period of glucocorticoid stratification (21, 22). Four chambers were implanted subcutaneously in each monkey immediately after cholecystectomy via bilateral paramedian incisions. The chambers were harvested in pairs 2 and 3 wk later. One chamber was fixed in 10% phosphate-buffered formalin, sectioned at 5 μ, stained with hematoxylin and eosin, and rated for degree of inflamation by a single investigator in a blind fashion. The second chamber was frozen on dry ice and stored at −70°C for hydroxyproline assay. The tissue was subsequently extracted, hydrolyzed, and analyzed on a 121 MB amino acid analyzer (Beckman Instruments, Inc., Spinco Div., Palo Alto, CA) (23).

Statistical analysis. Results are expressed as the mean±SE. Survival data were compared by the chi-square method. Simultaneous group comparisons at each time point were independent and complied to parametric testing. Thus, analysis of variance, as suggested by Bonferroni, was performed (24). Since serial within-group values were interdependent, the nonparametric Wilcoxon Rank Sum Score employing the Kruskal-Wallis test, was used to evaluate within-group changes over time (25). The wound healing data were compared using Duncan's multiple range test (26).

Results

The magnitude of surgical stress, as assessed by operative time and blood loss determinations, was similar in all groups. The reactions to this stress differed markedly among the groups.

Survival. The survival data are presented in Fig. 2. No deaths occurred during the adrenalectomy, 4-mo recovery phase, or 4-d glucorticoid dose stratification period. There were no deaths in the sham adrenalectomy-placebo group. The subphysiologically replaced group experienced a 38% mortality rate (three deaths), which was higher than the sham adrenalectomy group ($P < 0.05$). One of the deaths occurred in the operating room during precholecystectomy Swan-Ganz placement. This animal developed progressive hypotension, ventricular irritability, and cardiovascular collapse. The other deaths occurred 1 and 15 d postoperatively, with no apparent cause. Autopsies were unrevealing.

The mortality rates were identical in the supraphysiologically and physiologically replaced groups (14%) and were not significantly different from the sham adrenalectomy-placebo group. One death occurred in each of these groups 1 d postoperatively. Postmortem examinations failed to demonstrate surgical complications that could account for the deaths.

Hemodynamic responses. Initially, all groups were hemodynamically similar (Figs. 3 and 4). 4 d after glucocorticoid dose stratification, and immediately before cholecystectomy, the subphysiologically replaced animals demonstrated reductions in mean systemic blood pressure ($P < 0.01$), cardiac intake ($P < 0.05$), and left ventricular stroke work index ($P < 0.01$). The heart rate, although not statistically different from controls, was inappropriately low for the degree of systemic hypotension. There were no hemodynamic differences between the sham-adrenal-

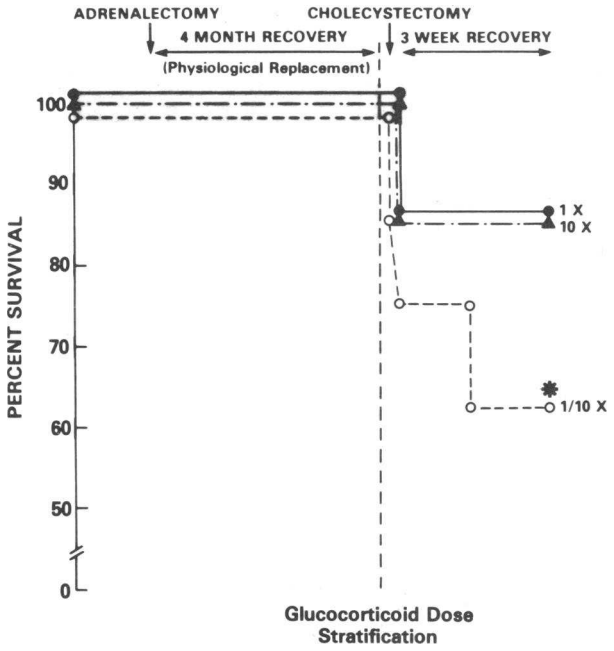

Figure 2. Survival curve depicted as percent survival in individual groups. Sham-adrenalectomy placebo group is indicated by the gray area (8/8 survivors). Glucocorticoid treatment groups represented by 1 time (physiological; 6/7 survivors), 10 times (supraphysiological; 6/7 survivors) and one-tenth time (subphysiological; 5/8 survivors) replacement. $*P < 0.05$ compared with control.

ectomy placebo, supraphysiologically treated, or physiologically replaced groups.

The postcholecystectomy hemodynamic evaluations demonstrated an amplification of the cardiovascular compromise noted in the subphysiologically treated group. The mean systemic blood pressure fell to a shock level (45 mm Hg). There was no evidence of congestive heart failure as the right atrial and pulmonary capillary wedge pressure were within the normal range (Fig. 3). There was, however, a significant decrease in the systemic vascular resistance index ($P < 0.05$) which was associated with a marked fall in the left ventricular stroke work index ($P < 0.05$) (Fig. 4). In spite of this peripheral vasodilation the animals did not become tachycardiac (Fig. 3).

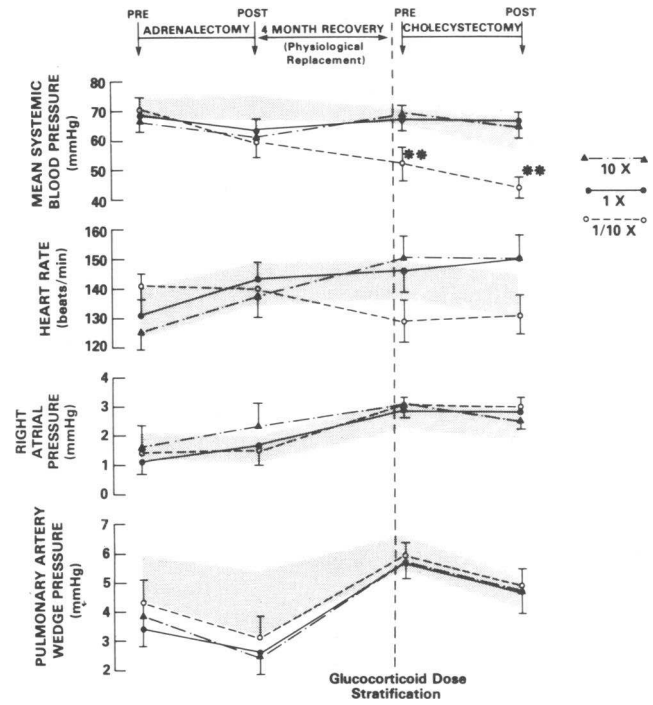

Figure 3. Hemodynamic responses pre- and postadrenalectomy and pre- and postcholecystectomy represented by the mean±SE for each group. Sham-adrenalectomy placebo response is indicated in gray. Dose of glucocorticoid replacement indicated by code in upper right. $*P < 0.05$, $**P < 0.01$ compared with control.

The physiologically replaced group, in contrast to the subphysiologically treated group, tolerated surgery with hemodynamic responses that were indistinguishable from either the sham adrenalectomy or the supraphysiologically treated group.

Hematologic and metabolic responses. There were no differences in hematocrit, hemoglobin, or platelet counts. Serum electrolytes, osmolality, blood urea nitrogen, creatinine, glucose, albumin, total protein, and calcium remained in the normal range after adrenalectomy and during glucocorticoid dose stratification (data not shown).

The subphysiologically replaced group demonstrated a relative neutropenia (57±4 vs. 81±3% neutrophils, $P < 0.05$) and eosinophilic leukocytosis (6.0±2.0 vs. 0.2±0.2% eosinophils, $P < 0.05$) 1 d after cholecystectomy when compared with the sham-placebo group. These leukocyte alterations were still apparent 2 wk after the operation did not occur in the other groups.

Although the subphysiologically replaced group did not demonstrate electrolytic abnormalities 1 d before or 1 d after cholecystectomy, significant changes were noted after an additional 2 wk of postoperative subphysiologic glucocorticoid replacement. This group developed a relative hyponatremia (140±1 vs. 145±1 mM/liter, $P < 0.01$) which was associated with azotemia (23±1.0 vs. 16±0.6 mg/dl blood urea nitrogen, $P < 0.05$), mild hyposmolality (296±8 vs. 303±5 mosmol/liter, $P < 0.08$), and hypoalbuminemia (3.2±0.1 vs. 4.0±0.1 gm/dl, $P < 0.01$). Metabolic derangements did not occur in the other groups.

Wound healing. There were no differences in wound healing as determined either by blinded histologic analysis of scar tissue (data not shown) or quantitative measurements of hydroxyproline formation (Fig. 5). All groups demonstrated progressive collagen formation between weeks two and three.

Discussion

The subphysiologically replaced group developed marked cardiovascular compromise, including hypotension with decreases in both the peripheral vascular resistance index and cardiac index. These manifestations are consistent with the known actions of glucocorticoids in permitting other hormones, such as the catecholamines, to maintain cardiac contractility and vascular tone (27–29). The hyponatremia noted in this group could not account for the hemodynamic instability observed, since it was not present at the time of surgery.

The physiologically replaced animals were indistinguishable from either sham-adrenalectomy placebo-treated controls or supraphysiologically treated primates. Thus, amounts of glucocorticoids equivalent to the daily (unstressed) cortisol production rate are both necessary and sufficient for primates to tolerate this form of surgical stress.

All groups healed in a similar fashion indicating that the supraphysiologic regimen of hydrocortisone used in our study

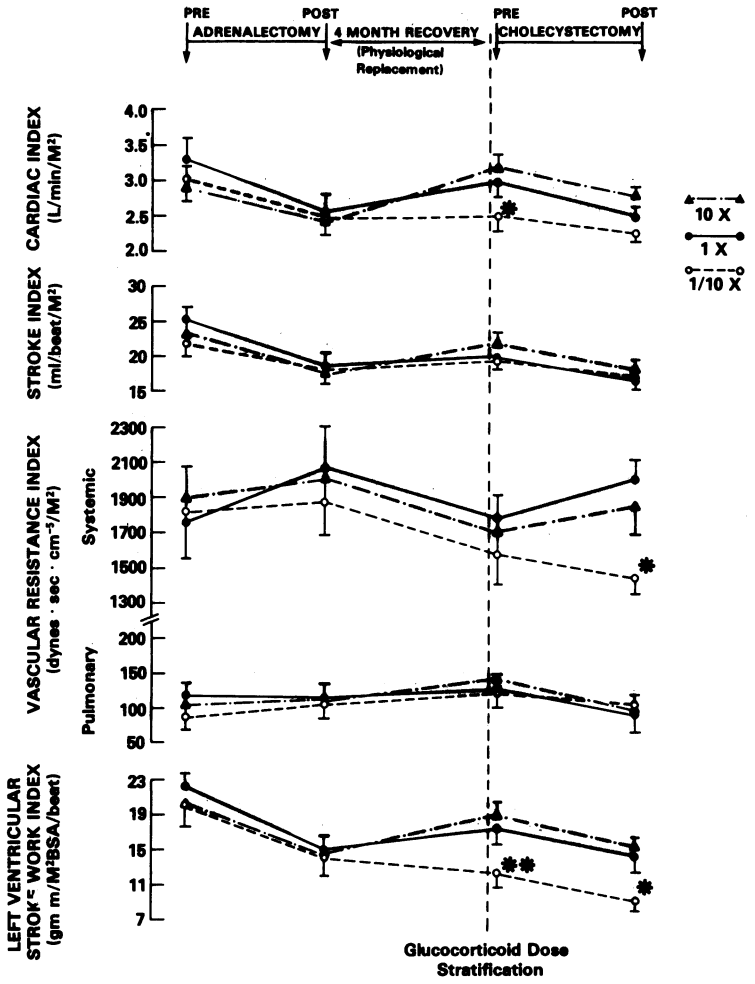

Figure 4. Hemodynamic calculations pre- and postadrenalectomy and pre- and postcholecystectomy represented by the mean±SE for each group. Sham-adrenalectomy placebo response indicated in gray. Glucocorticoid replacement dose indicated by code in *upper right.* $*P < 0.05$, $**P < 0.01$ compared with control.

did not inhibit collagen formation. This is in contrast to studies in the rat where similar doses of glucocorticoids inhibited wound healing (13). A possible explanation for this difference is that the rat is particularly sensitive to glucocorticoids (30). In addition to the lack of effects on wound healing, we did not demonstrate other signs of glucocorticoid excess in our supraphysiologically treated primates. We suspect that the known deleterious effects of high-dose glucocorticoids were not seen in this study because of the relatively short duration of treatment with a modest maximum dose.

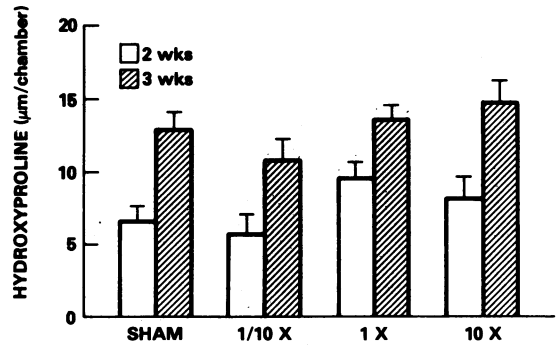

Figure 5. Hydroxyproline accumulation in wound chambers after 2 and 3 wk of stratified glucocorticoid treatment, expressed as the mean±SE. Each group demonstrated increased hydroxyproline formation between 2 and 3 wk. There were no significant differences among groups at either time point.

This study suggests that the increased secretion of cortisol, which is characteristic of stress, is not essential for survival. It is tempting to suggest that this familiar component of the stress response may be an epiphenomenon entwined with other essential biochemical events as yet unrecognized. For example, adrenocorticotropic hormone is derived from a large parent protein, proopiomelanocortin, which also serves as the source of β-lipotropin, melanin-stimulating hormone, β-endorphin and other proteins with as yet undefined biological roles (31). Could it be that the increased secretion of these peptides is essential for stress survival? In that case, the increase in adrenocorticotropic hormone and cortisol would be passive concomitants.

We conclude that there is no apparent advantage in supraphysiologic glucocorticoid prophylaxis during surgical stress in primates. Glucocorticoid doses equivalent to the daily unstressed cortisol production rate are sufficient to allow homeostatic mechanisms to function during surgery. On the other hand, the data from this study emphasize the liability of undergoing surgical stress in a state of adrenal insufficiency. Thus, while no benefit occurred with increased cortisol treatment, a clear disadvantage was associated with underreplacement. This suggests that the clinician must assure that the patient receives physiologic levels of replacement before the surgical event. Although the results of this study are unequivocal, we suggest that randomized prospective trials in patients with adrenal insufficiency should be

performed before changing the current glucocorticoid coverage regimens.

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