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Peri-operative Steroids

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INTRODUCTION

Steroids have a wide range of physiological functions, ranging from ensuring effective function of the autonomic nervous system, to regulation of the sleep-wake cycle, while also playing an integral part in the stress response to surgery. Steroids also play a major anti-inflammatory role and are now commonly used in patients' illnesses such as inflammatory bowel disease, sarcoidosis, rheumatoid arthritis, psoriasis, eczema, and reactive airways disease.

Not surprisingly then, it is common for patients on chronic steroid therapy to present for surgery. Whether these patients require perioperative steroid supplementation or not, and if so, what dose to give, remains a rather controversial topic. Furthermore, there is no class A or B evidence to support the current guidelines on perioperative steroid supplementation. The aim for this review is to discuss the physiological and clinical uses of glucocorticoids, and to review the guidelines for peri operative steroid supplementation in patients on chronic steroid therapy.

HISTORY OF CORTICOSTEROIDS

Steroids were first discovered in the early 1930s from plant extracts, by an American scientist named Percy Lavon Julian, who was the grandson of a slave. (1)By 1940, it was understood that two forms of steroids existed, namely glucocorticoids and mineralocorticoids, and in 1948 the first rheumatoid arthritis patient was treated with cortisone. Oral and intra-articular hydrocortisone injection began in 1950 and 1951 respectively. Between 1954 and 1958, the anti-inflammatory effects of steroids were introduced, and by 1960 all the toxic effects of chronic corticosteroid administration had been described. (1)(2)

In 1952, Fraser et al. wrote a case report on a 32 year old patient diagnosed with severe rheumatoid arthritis, who presented for a cup hip arthroplasty, and died three hours post operatively. The patient had been receiving daily cortisone 25mg orally for the last eight months prior to theatre, and had his steroids abruptly discontinued for two days before surgery. Intra-operatively he was found to have refractory hypotension, which did not respond to fluid therapy. However, no vasopressors were given to address the hypotension. The post mortem revealed bilateral adrenal gland atrophy, and thus the death was attributed to secondary adrenal insufficiency. (3)

A similar case report was published by Lewis et al. in 1953. A female patient had been receiving 75mg of cortisone daily for three months prior to presenting for repair of a flexion contracture of the left knee. She developed severe hypotension intra-operatively which did not respond to fluid therapy, and subsequently died five hours post operatively. A post mortem report showed bilateral adrenal haemorrhage with adrenal gland atrophy and secondary adrenal insufficiency was also attributed as the cause of death in this woman. (4)

Subsequently, both Lewis et al. and Fraser et al. recommended that patients who had been on chronic steroid therapy presenting for any surgery be given supplemental steroids. The type of surgery was not specified, neither was the dose of steroids at which patients would receive supplementation. They recommended 100mg of hydrocortisone pre-operatively, followed by 100mg for the subsequent three days post operatively. No rationale was given for this recommended dosage regimen. (3, 4)

These recommendations were followed for the next four decades, until Glowniak et al. published a randomized, double-blinded study in 1997. This study was conducted to determine whether patients receiving supraphysiological chronic steroids required peri-operatively steroid supplementation or not. It was the results of this study which paved the way for the currently ongoing debate on perioperative steroid supplementation: should steroids be given peri-operatively, and if administered, what dose would be considered adequate? (5)

PHYSIOLOGY OF CORTICOSTEROIDS

Glucocorticoids regulate a range of physiological functions, including an important role in the stress response to surgery. Cortisol is the main glucocorticoid produced by the adrenal gland, comprising 80% of the total glucocorticoids produced. Corticosterone comprises less than 20% of the glucocorticoids produced.(6)

The hypothalamic pituitary axis

The production of glucocorticoids is regulated by the hypothalamic-pituitary-adrenal axis (HPAA), as shown in the figure 1.

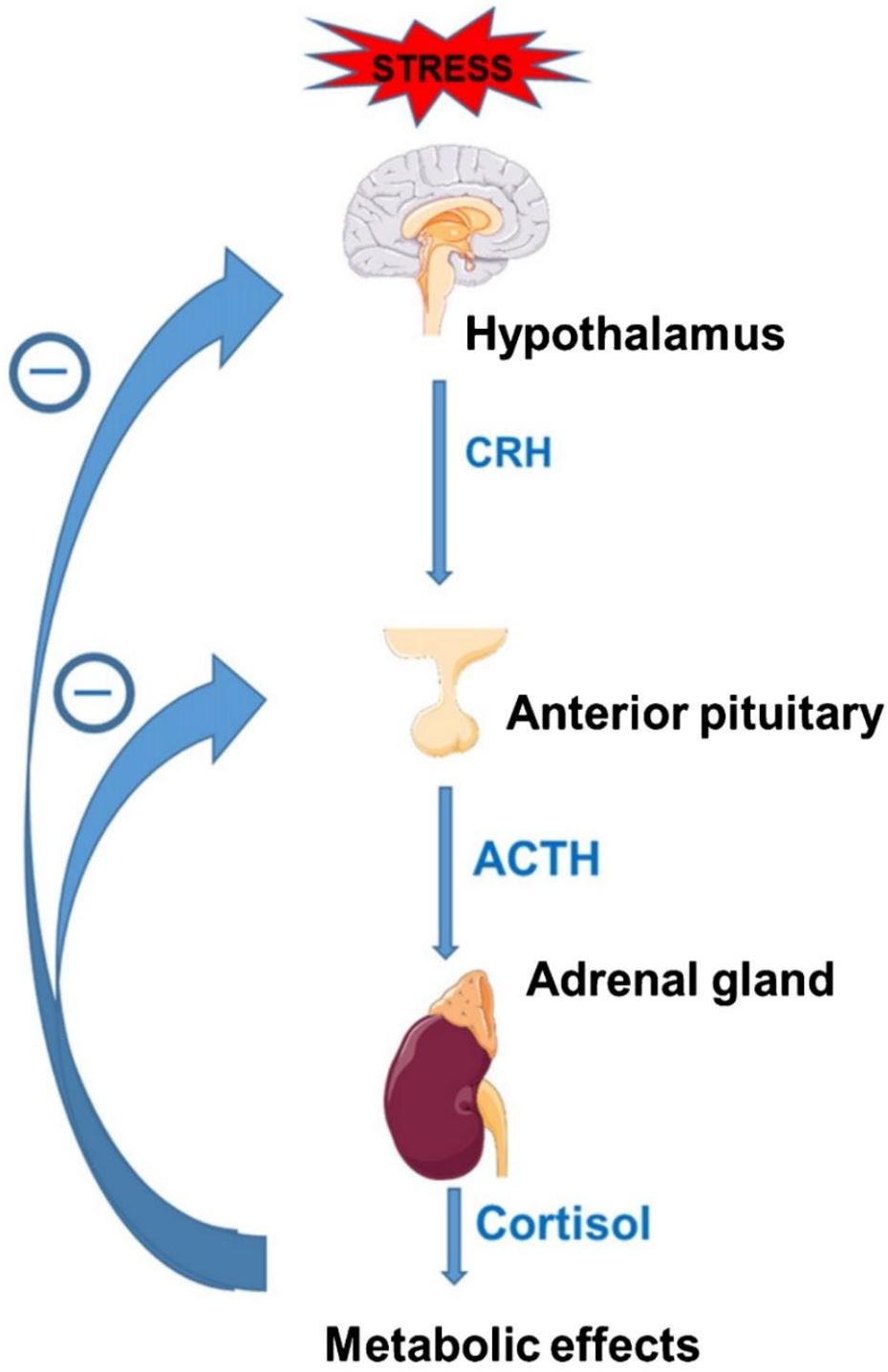


Figure 1. The hypothalamic-pituitary-adrenal axis (HPAA). *(Extracted from Management of adrenal insufficiency risk after long term systemic glucocorticoid therapy in Duchenne muscular dystrophy: clinical practice recommendations, a review article by Bowden et al.)* (6, 7)

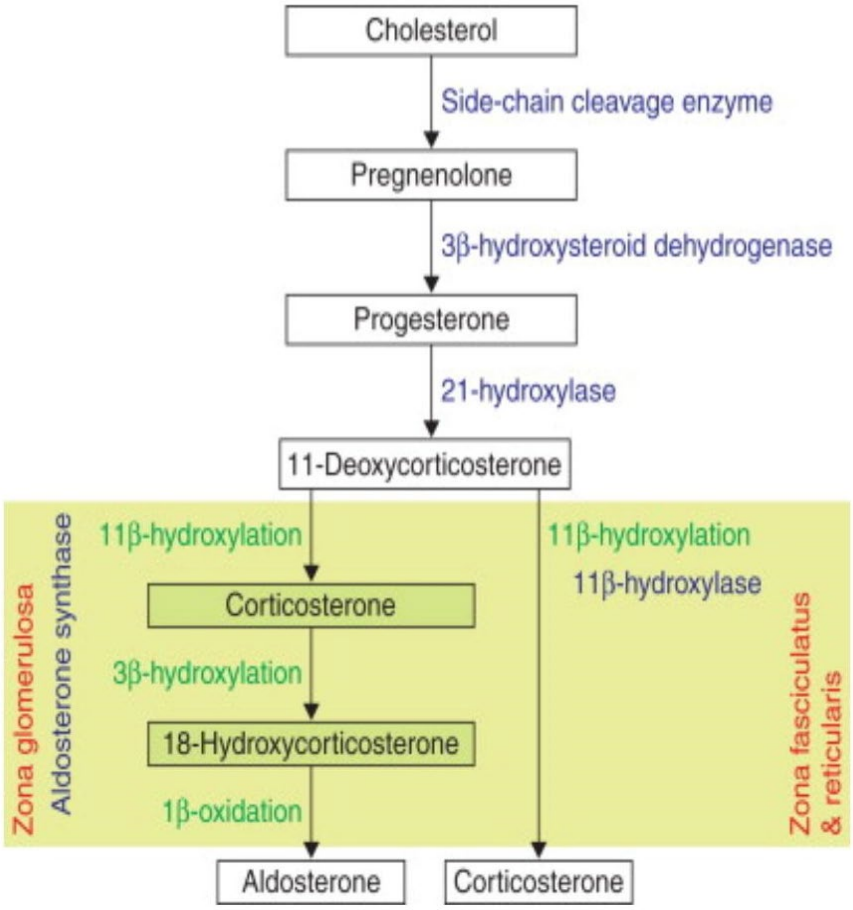
The axis, like many others in the body, is regulated by a negative feedback mechanism, with release of the cortisol inhibiting further release of adrenocorticotropic hormone(ACTH) from the anterior pituitary and corticotropin releasing hormone(CRH) from the hypothalamus.(6, 7)

Glucocorticoid production within the adrenal cortex

Within the adrenal cortex, the synthesis of glucocorticoids follow the pathway shown in figure 2. Note although the end hormone shown in the figure is Corticosterone, cortisol follows the same enzyme pathway.

Figure 2. The production of Corticosterone. *(Extracted from Surgical endocrinopathies, adrenal physiology by Jessica Furst and Salila Kurra, 2015)*(8)

As earlier stated, cortisol is the major glucocorticoid produced. It circulates in the blood bound to cortisol-binding globulin (80%) and albumin (15%), and only the free fraction (5%) of it is physiologically active. (9)



Cortisol release is influenced by many factors and exhibits a diurnal circadian rhythm in its production. 75% is released into the bloodstream in the morning, and a small amount is released in the evening. Patients who are receiving glucocorticoid supplements also exhibit this diurnal secretion of cortisol. Up to 20mg of cortisol is produced each day. (10, 11)

The following factors increase the production of cortisol:

- Physical stress e.g. surgery, physical trauma, exercise, haemorrhage
- Psychological stress e.g. anxiety, fear, pain
- Physiological stress e.g. nausea, hypoglycaemia (11)

Factors affecting the production of mineralocorticoids, namely, high potassium intake, low sodium levels, posture, etc. do not affect the production of corticosteroids.

PHYSIOLOGICAL ROLE OF GLUCOCORTICOIDS

Glucocorticoids have a wide range of physiological effects. These are summarized in Table 1 below.(11).

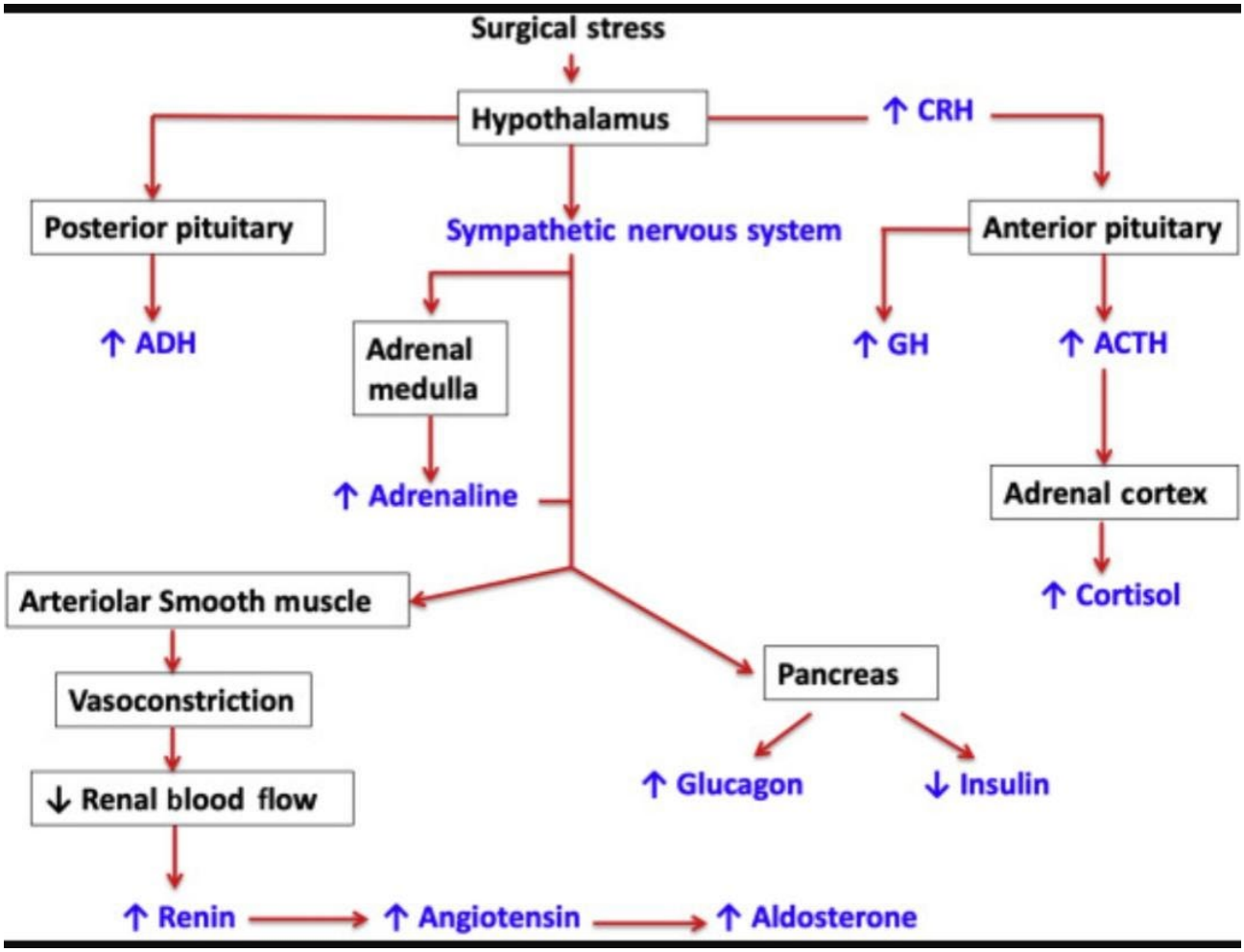
Table 1. The physiological role of glucocorticoids

Organ System	Role of cortisol
Central nervous system	Regulation of sleep- wake cycle Regulate the brain's ability to adapt to stress Alter neural plasticity Affect ability to learn and memory
Cardiovascular system	Regulation of beta receptors Increases blood vessels sensitivity to catecholamines Positive ionotropic effects
Respiratory System	Production of pulmonary surfactant
Gastro-intestinal system	Increases pepsin and gastric acid secretion
Foetal Development	Maturation of liver enzymes Production of pulmonary surfactant
Metabolism	Has an overall anti-insulin effect Decreases muscle glucose uptake by interfering with Glut 4 translocation receptor into the cell membrane Decreases glucose utilization by the NADPH oxidation Increases transcription of mRNA for enzymes involved in gluconeogenesis Increases protein catabolism
Bone	Increases osteoporosis by decreasing osteoblastic activity Increases collagenase activity
Immunity	Anti-inflammatory effects: Causes stabilization of lysosomes, thus decreasing proteolytic activity Decreases capillary permeability, thus reducing diapedesis of leukocytes Interferes with complement pathway Acts as a potent immunosuppressant by decreasing phospholipase A2
Haematological	Increases production of RBC, neutrophils, platelets Decreases lymphocyte production

THE SURGICAL STRESS RESPONSE

Figure 3. The surgical stress response. *(Extracted from BJA review article, Anaesthesia, analgesia, and the surgical stress response, July 2020)*(12)

In stressful situations, the adrenal glands produce 10X the normal cortisol levels. The amount of cortisol produced depends on the type of surgical stress, with open major surgery and a general anaesthetic producing a greater surgical stress response as compared to a closed minor surgery and regional anaesthesia, respectively. (6)



The rate-limiting step for the production of cortisol in the adrenal cortex is the conversion of cholesterol to pregnenolone by the enzyme desmolase. The enzyme 11 beta hydroxylase is rapidly inhibited by the administration of a single dose of etomidate. However, detailed in vivo studies have not suggested that this produces any clinically relevant changes if given as a single dose. Adverse outcomes are reported when etomidate is administered as an infusion, something no longer done in clinical practice.(9)

ADRENAL INSUFFICIENCY

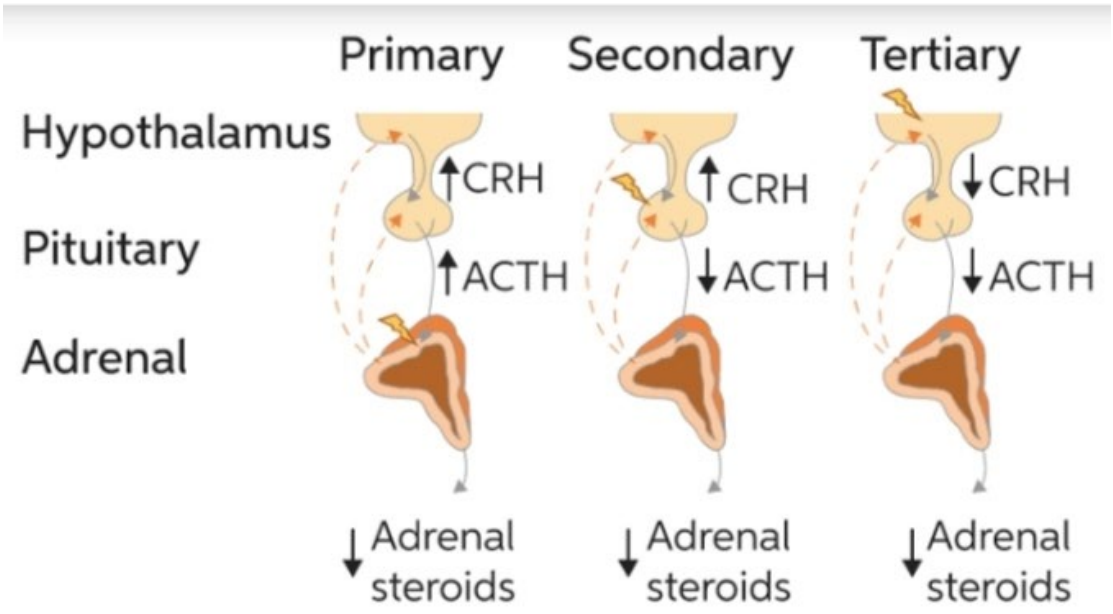


Figure 4. Types of adrenal insufficiency. *(Extracted from Adrenal insufficiency by Nicolaides N.C, Chrousos G.P, Charmandari E. 2014)* (13)

Insufficient cortisol production occurs in patients with adrenal insufficiency, which can be either primary or secondary. Primary adrenal insufficiency is when the adrenal glands fail to produce glucocorticoids and mineralocorticoids and can be due to a host of disease processes including autoimmune diseases. Secondary adrenal gland insufficiency occurs in patients who have been receiving exogenous steroids, and only affects the gland's ability to produce glucocorticoids. Mineralocorticoid production is unaffected. Tertiary adrenal insufficiency is when the hypothalamus fails to produce CRH, and is often classified as secondary adrenal insufficiency. (14)

Insufficient cortisol production results in progressive loss of vasomotor tone as a result of a decreased sensitivity of the alpha-adrenergic receptors to circulating catecholamines. A resultant progression of symptoms then ensues, with orthostatic hypotension being the first, followed by supine hypotension and then shock. In the anaesthetized patient, the first symptom noted is a progressive decline in blood pressure, with an accompanying increase in the pulse rate. (9)

PHARMACOLOGY OF CORTICOSTEROIDS

Comparing potencies

Different formulations of glucocorticoids are found, and the following table extracted and modified from Milner and Welch's Applied Pharmacology in anaesthesiology and critical care, summarizes the different preparations.

Table 2. Comparing potencies of different glucocorticoids

Corticosteroid	Glucocorticoid effect	Mineralo-corticoid effect	Dose equivalent to 5mg prednisone	Half-life (hrs)	Route
Hydrocortisone	1	1	20mg	6-8	PO, IV, IM
Prednisone	4	0.1-0.2	5mg	18-36	PO
Methylprednisolone	5	0.1-0.2	4mg	18-36	IV
Dexamethasone	30	<0.1	750ug	36-54	PO, IV
Fludrocortisone	0	20	-	18-36	PO

Clinical uses of corticosteroids

As mentioned earlier, glucocorticoids have a wide range of uses in many diseases, and as such each discipline can possibly write a book on the effects on glucocorticoids in their field.

Of importance to the anaesthetist, is the use of glucocorticoids in clinical medicine for the management of Chronic obstructive pulmonary disease (COPD) and in asthmatic patients, in psoriasis, eczema, rheumatoid arthritis, sarcoidosis, dermatitis, systemic lupus erythematosus and of course, more recently in the management of covid pneumonia.

Glucocorticoids have been shown to reduce the reactionary cerebral oedema seen in patients with intra-cranial tumors, but do not help with the oedema associated with head injury patients.

Anaesthetic uses of glucocorticoids:

1. Anti- inflammatory – dexamethasone is used to prevent airway oedema in susceptible patients e.g. tonsillar surgery, debulking of airway papillomas, maxillofacial surgery, repetitive instrumentation of the airway
2. Analgesia- dexamethasone at 0.05 – 0.1mg/kg
3. Prevention of post operative nausea and vomiting- dexamethasone at 0.1-0.2mg/kg prevents post operative nausea and vomiting
4. Adjunct in septic shock- patients with refractory hypotension, poorly responding to vasopressors and fluid therapy may benefit from hydrocortisone 50mg 6 hourly, a total of 100mg per day, or 100mg bolus dose followed by 10mg/hr infusion.
5. Acute respiratory distress syndrome (ARDS) – use remains controversial, but recent evidence points towards the benefit of glucocorticoids in reducing number of days spent on the ventilator, and reducing the overall mortality of patients with ARDS (11)
6. Covid 19- recent evidence has shown a benefit of glucocorticoids in patients with severe covid pneumonia requiring oxygen supplementation, whilst no benefit has been shown in those patients with mild forms of the disease

(15)

SIDE EFFECTS OF CHRONIC STEROID THERAPY

Steroids are associated with several side effects, and the table below shows the common side effects that are relevant to the anaesthetist.

Table 3. Side effects associated with chronic steroid use

System	Side effects
Endocrine	Cushingoid syndrome Glucose intolerance Growth Hormone inhibition resulting in stunted growth in children Adrenal insufficiency
Cardiovascular	Hypertension Oedema secondary to sodium retention which may lead to congestive heart failure
Metabolic	Cushingoid syndrome. The persistent hyperglycaemia results in persistently elevated insulin levels, which leads to lipogenesis. The fat is then deposited centrally, resulting in a moon face, truncal obesity and a buffalo hump
Skin	Thin skin which bruises easily (particularly important when applying strapping, and eye protection as skin may be easily damaged on removal of such adhesive tapping) Bright red cheeks Striae especially around the abdominal areas Allergic contact dermatitis Peri-oral dermatitis
Muscle and bone	Loss of muscle mass Muscle weakness secondary to hypokalaemia Osteoporosis Calcium reabsorption is inhibited with secondary hyperparathyroidism Vertebral fractures (care when positioning patients and when extending the neck during intubation)
CNS	Euphoria Anxiety Manic depressive episodes Withdrawal syndrome after long term administration with sudden cessation of the steroids
Electrolyte abnormalities	Hypokalemic metabolic alkalosis Sodium and water retention
Gastrointestinal	Predisposition to peptic ulcer disease

CONTROVERSIES

The debate as to which patients on chronic steroids should receive steroid replacement therapy, and the dose to be given is an ongoing debate. The current guidelines lack class A and B evidence to fully endorse them and may therefore change as more studies are done.

In 1973, Kehlet and Binder performed a study on adrenocortical function and clinical course during and after surgery in unsupplemented glucocorticoid-treated patients, using 73 patients on chronic steroids prednisone per day. Patients presenting for both major and minor surgery were enlisted, and steroids were withheld for 36 hours pre-operatively, and for 24 hours post operatively. Plasma cortisol levels were measured, as were the vitals, and they found unexplained hypotension in 7 out of 18 patients.

Of the 7 patients, only 3 had low cortisol levels when measured, and the hypotension was unresponsive to rescue cortisol therapy. They concluded that, “pre-operative plasma cortisol was not the prime determinant of the level of blood pressure in the glucocorticoid treated patients during and after surgery, and acute stress induced adrenocortical insufficiency is rare even when steroids are withheld.” (16)

In 1997, Glowniak *et al.* conducted a double-blinded study of peri-operative steroid requirements in secondary adrenal insufficiency patients. This study had a total number of 17 participants, with one patient entered twice. All study participants were male, and all had been clinically treated with glucocorticoids for at least two months prior to presenting for theatre. A pre-operative test for adrenal insufficiency was done using a rapid ACTH stimulation test. Baseline cortisol levels were drawn up prior to the patient being administered cosnytropin. Adrenal insufficiency was defined as a 60-minute interval cortisol level of less than 550nm/L. Patients taking 5mg of prednisone were found not to have adrenal insufficiency, and were therefore withdrawn from the trial.

The first group of patients was given supplemental corticosteroids in accordance with guidelines at the time: 200mg of cortisol for the first 24 hours, followed by 100mg on the second day, and 50mg on the third day. These were given on top of the normal daily dose that the patient was receiving. The second group of patients received only their normal daily dose of steroids, and normal saline.

Using the difference between the maximum and minimum systolic blood pressures intra-operatively, and the maximum pulse rates obtained, they found that only one patient who underwent a splenectomy had a significant, 5-minute intra-operative hypotensive period, with a blood pressure of 80/40mmHg. This rapidly responded to fluid replacement. This patient was in the placebo group. One other patient in the steroid treated group experienced acute, severe post operative hypotension with a blood pressure of 74/50mmHg. He was given cortisol and removed from the study.

Glowniak *et al*. concluded that patients with secondary adrenal insufficiency as a result of chronic steroid therapy do not experience hypotension in the absence of stress dose steroid administration and can be maintained on their usual daily dose of steroids in the peri-operative period. (5)

A 2013 Cochrane review stated: “Currently there is inadequate evidence to support the use of supplemental peri-operative steroids in patients with adrenal insufficiency. It is likely that in the majority of adrenally suppressed patients undergoing surgery, administration of the patient’s daily maintenance dose of corticosteroid may be sufficient and that supplemental doses are not required.” (17)

Controversy also arose as to which patients required pre-operative adrenocortical function. Marik and Varon concluded that most patients do not need pre-operative adrenocortical function evaluation tests unless it would affect peri-operative function. (18)

Recent data suggests that patients receive their usual dose of steroids with vigilance to the signs and symptoms of adrenal insufficiency intra-op. conservative means of intra-op hypotension should be initially applied, namely, replacing fluid losses, decreasing the depth of anesthesia, use of vasopressors and management of metabolic abnormalities like a hypocalcaemia on a blood gas. (19)

CURRENT RECOMMENDATIONS ON REPLACEMENT OF STEROIDS

Regardless of all the Controversies available, current guidelines recommend steroid replacement for patients who are classified as at high risk for secondary adrenal insufficiency. Woodcock etal published the most recent recommendations on peri-operative use of steroids in 2020.

Risk stratification

Table 4. Risk stratification of patients for peri-operative steroid replacement.

Patient	Definition	Recommendation
Low risk	Taking any dose of glucocorticoids for less than 3 weeks Prednisone 5mg od morning dose Prednisone 10mg po every other day	Do not need an ACTH stress test. Do not need stress dose steroid supplementation
Intermediate risk		Send for an ACTH stress test Apply clinical judgement as to whether or not to give steroid stress dose supplements
High risk	Patients with clinical Cushing's syndrome Receiving >20mg prednisone or equivalent for >3 weeks Diagnosed with secondary AI Patients applying highly potent topical steroids to a large body surface area for a prolonged period of time.	Give stress dose administration

(6)

Hydrocortisone remains the drug of choice when supplementing glucocorticoids in the high-risk patients due to its glucocorticoid-mineralocorticoid ratio. As shown in the table above, risk stratification of patients on steroids is the first important step. All patients stratified as low risk need not have steroid supplementation, and do not need to be tested for adrenal insufficiency. All low risk patients can continue their usual daily dose of steroids as scheduled.

Patients classified as intermediate risk, that is those patients who do not fit the low risk criteria, nor the high risk criteria, can be managed in accordance with the clinicians judgment. If time and resources allow, such patients can be sent for an ACTH stress test, or else clinical judgement can be used to determine whether or not to supplement them.

Development of adrenal suppression can also occur in patients applying topical steroids, those taking inhaled steroids, and those receiving intra-articular injections. Development of adrenal suppression from inhaled steroids is related to the dose, the duration of therapy and the use of a potent agent. Patients taking these agents can be risk stratified on an individual basis.

The current recommendations are to supplement the steroids in patients who have demonstrated HPAA suppression, as evidenced by the ACTH stimulation test, or those patients in the high risk category. Patients with a normal response to the ACTH stimulation stress test do not require supplementation.

Steroid supplementation

Adults:

Major surgery/ caesarian section

- 100mg iv hydrocortisone at induction, followed by an immediate infusion of 200mg iv administration over the next 24 hours If an infusion is not possible, hydrocortisone 50mg intramuscularly can be given every 6 hours.
- Single dose dexamethasone 6-8mg IV at induction is a safe alternative
- Post operatively, an infusion of hydrocortisone 200mg over 24hrs can be administered
- Or alternatively 50mg IMI
- Enteral glucocorticoids can be resumed at double the pre-surgical therapeutic dose for 48hrs if recovery is complicated, or alternatively double the oral dose for up to 1 week post-op.

Body surface and intermediate surgery

- Intra-operatively replace as with major surgery. Dexamethasone 6-8mg intravenously if used, will suffice for 24 hours.
- Post operatively double the regular glucocorticoid dose for 48 hours, then continue usual treatment dose if uncomplicated.

Bowel procedures requiring laxatives or enema

- Continue normal glucocorticoid dose, or give equivalent iv dose if prolonged nil per mouth.

Labour and vaginal delivery

- Hydrocortisone 100mg intravenously at onset of labour, followed by an immediate initiation of an infusion of hydrocortisone 200mg over 24 hours.
- Alternatively, give hydrocortisone 100mg intramuscularly followed by 50mg intramuscularly every 6 hours.

Children:

Major surgery

- Hydrocortisone 2mg/kg at induction, followed by an immediate infusion based on body weight, 25mg over 24 hours for up to 10kg weight; 50mg over 24 hours for 11-20kg; and those over 20kg, pre-pubertal 100mg per 24 hours, and pubertal 150mg per 24 hours.
- Post operatively, child should receive double usual oral dose of hydrocortisone for 48 hours, and then reduce to normal doses over up to a week.

Minor surgery requiring general anaesthesia

- Hydrocortisone 2mg/kg intravenously or intramuscularly at induction of anaesthesia is adequate.
- Double normal hydrocortisone doses once enteral feeding is established and continue on double dose for 24 hours

Minor procedures not requiring general anaesthesia

- -Double morning dose of hydrocortisone given pre-operatively
- -Post operatively resume normal dose of hydrocortisone. (9)

CONCLUSION

The recommendations for peri-operative steroid supplementation remain a controversial subject because of lack of class A and B evidence to support the current guidelines and may be subject to further change as more evidence emerges. A pragmatic approach to adrenal replacement during major stress is required.

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