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Perioperative care in hypoadrenalism: A narrative review

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Highlights

- Amongst the many causes of adrenal insufficiency, primary adrenal failure or Addison's disease is an important cause of hypoadrenalism.
- Adreanl insufficiency is a common medical problem in surgical patients and can cause preventable major ad verse events.
- It is important to identify patients at high-risk of adrenal insufficiency and to give appropriate replacements perioperatively.
- Current guidelines clearly outline the required amount of steroid dose during the intraoperative and postopera tive period in patients with insufficient adrenal function.

Abstract

Impaired production of adrenal hormones or hypoadrenalism is not uncommon and has various aetiologies. Untreated hypoadrenalism during operative period can lead to preventable major adverse events. Identification and risk stratification in those who have hypoadrenalism is an important part of preoperative assessment. There are multiple guidelines on intraoperative care and anaesthesia for patients with adrenal insufficiency. The aim of this review is to discuss the available evidence and optimal management approaches for surgical patients with hypoadrenalism during intra- and post-operative periods.

Keywords: Hypoadrenalism, adrenal insufficiency, perioperative care, surgery

Introduction

Adrenal insufficiency or hypoadrenalism is not uncommon in surgical patients. Hypoadrenalism can be primary, secondary or tertiary. Diseases in adrenal gland such as infarction, infection or tumour can cause primary hypoadrenalism. Addison's disease is a rare primary endocrine disease of the adrenal gland that affects 10 in 100,000 people across the world [1]. Its incidence in Australia is about 100 new diagnosis per year with 2,500 affected across the country [2]. Other situations with adrenal insufficiency are secondary hypoadrenalism from hypopituitarism or adrenocorticotropic hormone (ACTH) axis suppression. Patients with adrenal insufficiency require lifelong glucocorticoid therapy to maintain vital body functions including balanced immune system, cardiovascular system and glycaemic metabolism [3]. The maintenance dose of glucocorticoid therapy is not sufficient in stress situations [4]. Perioperative period is associated with significant stress to the human endocrine system, and extra glucocorticoid supplementation is essential throughout this period. However, a limited number of universally accepted guidelines are available on glucocorticoid supplementation during perioperative period for patients on longer term replacements. The aim of this review is to summarize current consensus on perioperative management of adrenal insufficiency.

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Table 1. Adrenal hormones / catecholamines and their function

Adrenal gland	Zone	Hormone category	Compound	Function
Cortex	Glomerularis	Mineralocorticoids	Aldosterone	Salt and water regulation
	Fascicularis	Glucocorticoids	Cortisol Cortisone Corticosterone	Glucose metabolism Immune modulation Vascular effect
	Reticularis	Androgens	Dehydroepiandrosterone	Masculinization
Medulla		Catecholamines	Epinephrine Norepinephrine	Stress response

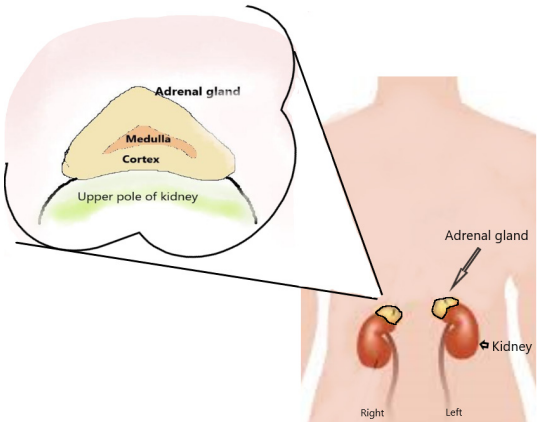

Figure 1. Anatomy of the adrenal gland.

Pathophysiology of adrenal insufficiency

There are two adrenal glands in human body. They are located over the superior pole of both kidneys and are also known as suprarenal glands [1]. Each gland consists of an outer cortex and an inner medulla (See **Figure 1**). The cortex is developed from mesothelial cells, and the medulla is derived from the neural crest which belongs to the ectoderm embryologically [3]. These two small glands produce several hormones that are responsible for regulating multiple physiological functions including blood pressure, metabolism, and immunity. The embryological development of the gland is related to its function.

Adrenal cortex produces corticosteroid hormones which are released in response to hypothalamic and pituitary hormones. The main corticosteroid hormones are glucocorticoids, mineralocorticoids, and androgens. On the other hand, the adrenal medulla produces catecholamines in response to sympathetic stimulation. These are epinephrine and norepinephrine, also known as adrenaline and noradrenaline [4]. **Table 1** further describes the function of the adrenal hormones and catecholamines.

Inability of adrenal gland to produce appropriate amounts of these hormones (**Table 1**) leads to adrenal diseases. This could either be hormone deficiency or excess. Primary adrenal insufficiency is low levels or absence of glucocorticoids production. This is also known as Addison's disease because it was first described by Thomas Addison [5]. The commonest cause for Addison's disease was tuberculosis at that time. However multiple causes are responsible for adrenal insufficiency and the commonest one is autoimmune adrenalitis (See **Table 2**) [6]. Autoimmune adrenalitis affects primarily the adrenal cortex. The pathogenesis involves both humoral and cell mediated immune mechanisms. Furthermore, other autoimmune disorders, such as polyglandular autoimmune syndrome type 1 and 2, are identified in about half of the patients with autoimmune adrenalitis [7, 8].

The diagnosis of adrenal insufficiency is based on ACTH stimulation test or "synacthen test" in suspected patients with clinical symptoms and positive basic laboratory tests [9]. Imaging studies and adrenal antibodies are used to identify the cause for adrenal insufficiency. Glucocorticoid replacement is the treatment of choice [9].

Preoperative assessment

The perioperative period exerts significant stress on the human body secondary to a number of factors, such as hypoxia, tissue inflammation, altered body fluids, and anaesthetic drugs. This perioperative stress activates the hypothalamic pituitary adrenal axis, which can be seen during various surgical procedures [10, 11]. As a result, glucocorticoid (cortisol) levels are increased perioperatively. However, the hypothalamic pituitary adrenal response is not consistent throughout the perioperative period with maximal ACTH and cortisol levels being recorded at the time of extubating or recovering from anaesthesia [10-12]. Furthermore, the cortisol levels slowly decline to normal in about 48 to 72 hours, while ACTH declines faster, within 24 hours [11, 12]. Cortisol has many vital functions during stress periods, including modulation of carbohydrate-protein-lipid me-

Table 2. Causes of adrenal insufficiency

Mechanism	Pathology
Autoimmune	Autoimmune adrenalitis
Infective	Bacterial -Tuberculosis
	Fungal infection- Histoplasmosis
	Spirochaete- Syphilis
	Viral- HIV
	Parasitic- Trypanosomiasis
Drugs	Rifampicin, Ketoconazole, Fluconazole, Phenytoin, Barbiturate
Malignancy	Lymphoma, Primary Breast/Lung/gastrointestinal cancer
Vascular	Bleeding or infarction of adrenal
Other	Congenital adrenal hypoplasia, Adrenoleukodystrophy, Amyloidosis

tabolism, maintenance of vascular tone and endothelial integrity, immune modulation, and potentiation of catecholamine action [13]. Patients with adrenal insufficiency (with or without cortisol replacement) lack this response and require extra doses to meet the demand during the perioperative period. Hypoadrenalism increases perioperative mortality and morbidity, particularly in those who develop adrenal crisis [14]. Perioperative management strategies for patients with adrenal insufficiency is crucial to minimize complications. The initial step of the management is preoperative evaluation of the adrenal disease.

Those patients diagnosed with Addison's disease, but are not on glucocorticoid replacements, necessitate assessment of their adrenal function and commencement of replacements as early as possible. Other patients with high degree of clinical suspicion for hypoadrenalism, require full workup to assess adrenal function as well as investigations to assess the causes (**Table 2**) [15]. Early initiation of cortisol treatment is advisable to achieve stable adrenal function by the time of surgery. However, clear guidelines regarding the recommended interval between treatment initiation and the surgical intervention are limited. In such cases, seeking endocrinology opinions from a specialist are warranted. Patients with a diagnosis of Addison's disease and on cortisol replacement, require close assessment in a preoperative or booking clinic. History of cortisol management, previous adrenal crisis details, medication adjustment strategies used in the past, and operative history should be taken in detail as a part of preoperative consultation. Collaboration with the patient's endocrinologist is the best practice [15-18]. There are no absolute contraindications for elective surgical procedures in individuals with adrenal insufficiency. However, clinical stability of the adrenal pathology is important with endocrinologist involvement in high-risk surgeries. Extra monitoring is recommended for day procedures.

Patients on glucocorticoid replacement could develop side effects from excess steroid levels. A detailed examination should be performed to look for Cushingoid signs. One of the commonest adverse effects of steroid therapy is immune suppression. This is through genomic mechanisms which suppress synthesis of proinflammatory cytokines, including interleukins, prostaglandins, and interferons, predominantly in chronic supratherapeutic use of steroids [18]. Steroid-induced myopathy and osteoporosis are well known adverse effects of excess steroid therapy. Dose-dependent increases in fasting and postprandial glucose levels and development of diabetes are rare in Addison's disease. However, type 1 diabetes is reported in 12% of individuals with Addison's disease secondary to autoimmune adrenalitis [7]. Other associated endocrine disorders, such as hypothyroidism (autoimmune polyglandular syndrome type 2) and hypoparathyroidism (autoimmune polyglandular syndrome type 2) should be excluded, if not investigated previously [6, 7]. Routine cardio-respiratory risk stratification is recommended for patients with diagnosis of Addison's disease who have other comorbidities.

Intraoperative care and anaesthesia

Patients with Addison's disease require close monitoring during the operative period. The normal stress glucocorticoid response is absent or blunted in patients with Addison's disease, which can lead to multiple complications. Continuous secretion of ACTH from the pituitary with high serum cortisol and epinephrine was reported during anaesthesia and recovery [11]. Inadequate cortisol and adrenaline response leads to poor vascular tone and hypotension. Prolonged stress leads to shock, also called "adrenal crisis" [19]. This necessitates extra

Table 3. Current guidelines on perioperative care of Addison's disease

Guideline	Authors	Major recommendations
Endocrine Society Clinical Practice Guideline 2016	Bornstein SR et al., 2016 [2]	Stress dosing in adrenal insufficiency
Emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients	Arlt W et al., 2016. The Society for Endocrinology Clinical Committee [22]	Steroid emergency card
Surgical guidelines for Addison's Disease and other forms of adrenal insufficiency 2017	Wass et al., 2017. Addison's Disease Self-Help Group [23]	List the ten main types of surgical procedures with different level of steroid cover for each
Potentially Life Threatening Steroid Dependency, Steroids and Saline Requirements for Surgery and Dentistry 2017	The Canadian Addison Society 2017 [24]	Based on the UK Addison's Disease Self Help Group
Supplemental perioperative steroids for surgical patients with adrenal insufficiency 2012	Yong et al., 2012. [25] Cochrane Systematic Review	Supplemental perioperative steroids were not required during surgery for patients with adrenal insufficiency (small number of patients)
Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency 2014	Husebye ES et al., 2014 [26]	Recommendations on diagnosis therapy and follow up
Guidelines for the management of glucocorticoids during the perioperative period for patients with adrenal insufficiency	Woodcock et al., 2020. Guidelines from the Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology UK [17]	Describe guidelines for primary and secondary adrenal insufficiency during various operative procedures

doses of glucocorticoids for patients undergoing anaesthesia.

However, this intraoperative cortisol response is affected by many surgical and anaesthetic factors [20]. Adrenocortical secretion can be supressed in anaesthesia. Regional anaesthesia can suppress neural input to hypothalamus. Some anaesthetic medications, such as Etomidate, can directly suppress adrenal cortex [21].

Various guidelines and recommendations describe appropriate use of steroid therapy during operative procedures (See **Table 3**). Amongst these, the guidelines from the "Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology United Kingdom" is used in most perioperative services across Australia [17]. This guideline recommends a loading dose followed by infusion of hydrocortisone at the time of induction in patients with primary or secondary adrenal insufficiency. The Hydrocortisone infusion is advised to continue until commencement of oral feed. Double of the regular dose of steroid should be commenced afterwards for up to 48 hours (See **Table 4**). Management of perioperative adrenal insufficiency in children is described in the guideline separately [17]. It is important to be aware that Dexamethasone is not appropriate glucocorticoid replacement in Addison's disease as it has no mineralocorticoid activity [17]. Therefore, this guideline clearly separates patients with adrenal insufficiency (primary or secondary) and patients receiving steroid therapy for other conditions, to avoid complications.

Despite glucocorticoid replacement therapy, acute adrenal insufficiency or adrenal crisis could develop in patients with Addison's disease during the perioperative period. Undiagnosed patients who are not on replacement are at high risk of experiencing adrenal crisis. Although the complete pathophysiology of adrenal crisis is not fully understood, it is possibly due to the lack of adrenal hormones to support the stress during surgery and anaesthesia. This can be a life-threatening condition if untreated [14]. Early identification is important to improve perioperative outcome in such patients.

Table 4. Adult perioperative steroid therapy for adrenal insufficiency

Severity of surgical stress	Primary and secondary adrenal insufficiency		Receiving adrenosuppresive doses of steroids (prednisolone equivalent ≥ 5 mg for ≥ 4 weeks)	
	Intra-operative	Post-operative	Intra-operative	Post-operative
Major surgery - Under anaesthesia (GA/LA) Include CS	HC 100 mg IV on induction followed by IV infusion of HC 200 mg/24 h	HC 200 mg/24h by IV infusion while NBM **Or** HC 50 mg 6 hly IM Resume oral – double HC doses for 48 h or for up to a week (with rapid recovery 24 h)	HC 100 mg IV on induction followed by IV infusion of HC 200 mg/24 h **Or** Dexamethasone 6–8 mg IV, if used, will suffice for 24 h	HC 100 mg/24 h IV infusion while NBM **Or** HC 50 mg every 6 hly IM Resume oral GC normal dose if recovery is uncomplicated. Otherwise, continue double oral dose for up to a week
Body surface and intermediate surgery	Same as above	Same as above	HC 100 mg, IV at induction, followed by IV infusion of HC 200 mg/24 h **Or** Dexamethasone 6–8 mg IV, if used, will suffice for 24 h	Double regular GC for 48 h, then continue usual dose if uncomplicated
Bowel procedures requiring laxatives/enema	Consider IV fluids and IV GC during preparation, HC 100 mg IV **Or** IM at the start of procedure	Resume enteral – double hydrocortisone doses for 24 h	Continue normal GC dose. Equivalent IV dose if prolonged NBM Treat as per primary adrenal insufficiency if concerned about hypothalamo-pituitary-adrenal axis function, and risk of adrenal insufficiency	
Labour and vaginal delivery	HC 100 mg IV at onset of labour, followed by IV infusion of HC 200 mg/24 h **Or** HC 100 mg IM followed by 50 mg 6 hly IM	Resume enteral – double hydrocortisone doses for 48 h	HC 100 mg IV at onset of labour, followed IV infusion of HC 200 mg/24 h **Or** HC 100 mg IM followed by 50 mg 6 hly IM	

Note: HC, Hydrocortisone; IV, intravenous; IM, intramuscular; GC, glucocorticoid; FC, fludrocortisone; NBM, nil by mouth; GA, general anaesthesia; LA, local anaesthesia; CS, caesarian section; hly, hourly.

Table 5. Management of adrenal crisis in adults

Immediate	Maintenance
1. **Hydrocortisone** immediate bolus injection of 100 mg hydrocortisone IV/IM followed by continuous IV infusion of 200 mg Hydrocortisone per 24 h **Or Hydrocortisone** IV/IM 50 mg 6 hourly 2. Rehydration with rapid IV 1000 mL of **isotonic saline** infusion within the first hour, followed by further IV rehydration as required (usually 4–6 L in 24 h; monitor for fluid overload in case of renal impairment and in elderly patients) • **Contact an endocrinologist**	• Tapering of hydrocortisone can be started after clinical recovery. • In patients with primary adrenal insufficiency, mineralocorticoid replacement (starting dose 100 micrograms fludrocortisone once daily) as soon as the daily glucocorticoid dose is below 50 mg hydrocortisone/24 h • Investigation of the underlying cause of disease

Clinical symptoms of adrenal crisis include low blood pressure, sudden abdominal or leg pain, vomiting, confusion, seizure, and lethargy. However, clinical assessment is limited during intraoperative and immediate post-operative period. Laboratory findings are more important perioperatively in suspected patients including hyponatremia, hyperkalaemia, hypoglycaemia, and hypercalcaemia. It's crucial to note that diagnostic tests should not delay the treatments of the condition [22]. The primary treatment of adrenal crisis is administration of glucocorti-

coids, specifically hydrocortisone (See **Table 5**) [23-27].

Postoperative management

Careful monitoring of patients with Addison's disease after surgical procedures is equally important as intraoperative care. Maintenance glucocorticoid therapy from intra-operative period needs to be continued based on type of surgery and recovery status (See **Table 4** and **5**). Prolonged hypotension and cardiovascular instability are reported in patients with adrenal insufficiency after surgical procedures [28]. Special attention is required in post-operative patients who are not taking oral diet, and glucocorticoid replacement should continue intravenously or intramuscularly as per recommendations [17].

Furthermore, patients with Addison's disease have issues with wound healing and immunity. Their wounds should be monitored closely, and a low threshold is recommended for septic screen if there is any evidence of postoperative infections [29]. Glycaemic monitoring is also important as the risk of hyperglycaemia is associated with excess steroid replacement, and hypoglycaemia is common with adrenal insufficiency [2].

Conclusion

Perioperative care with adequate glucocorticoid replacement is very important in patients with hypoadrenalism during operative procedures. These patients require additional glucocorticoid doses during surgery and anaesthesia. Current guidelines clearly outline the required amount of steroid dose during the intraoperative and postoperative period. Acute adrenal insufficiency or adrenal crisis is a life-threatening condition which could occur in patients with Addison's disease during surgery, and early identification and treatment to minimize complications and mortality are critical.

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