NARRATIVE REVIEW

Perioperative management of Endocrine disorders- practical considerations

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Abstract

It is important to correctly identify and treat endocrine conditions well before, during and proceeding surgery, even if this entails delaying surgical intervention. Failure to do this has been shown to increase mortality and morbidity. Hormones are involved in controlling metabolism, cellular processes, blood pressure, blood glucose levels, calcium homeostasis as well as fluid and electrolyte balance. Disordered hormonal production can be deleterious right from the time of anaesthesia induction. Specific endocrine disorders, such as thyroid disorders, pheochromocytoma, Cushings, adrenal insufficiency, acromegaly, hypercalcemia, carcinoids and diabetes insipidus have been discussed in literature, with practical considerations. This includes alternative modality of drug administration, management of associated comorbidities, as well as optimisation of nutrient levels pivotal to the success of bariatric surgery. For the current narrative review, a search on Google, PubMed, Up-to-Date and relevant clinical practice guidelines was carried out to extract the requisite information. Optimisation of the endocrinopathy and its sequelae, geared towards achieving metabolic control starting well before the procedure, is likely to lead to good surgical outcomes.

Keywords: Thyroid disorders, Pheochromocytoma, Cushings, Acromegaly, Hypercalcaemia, Hypocalcaemia, Carcinoids, Diabetes insipidus, Bariatric surgery.

DOI: https://doi.org/10.47391/JPMA.10756

Introduction

It is important to address endocrine conditions perioperatively. Failure to do this has been shown to increase mortality, morbidity and hospital stay.[1] Hormones are involved in controlling metabolism, cellular processes, blood pressure, blood glucose levels, calcium homeostasis, fluid and electrolyte balance. Hormonal derangement can be deleterious right from time of anaesthesia induction and then some. The current narrative review was planned to emphasise on practical considerations in the perioperative management of endocrine disorders. A search on Google, PubMed, Up-to-Date and relevant clinical practice guidelines was carried out to extract the requisite information.

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Submission completed: 30-10-2023 **1st Revision received:** 11-06-2024
Acceptance: 05-03-2025 **Last Revision received:** 04-03-2025

Specific disorder management

Pituitary

Prolactinomas are most common functioning pituitary tumours for which medical management is primarily indicated, even in case of chiasmal compression.[2] In case of giant macroadenomas (>3.5cm) serum prolactin, if reported as normal, prolactin in serial dilution may reveal a true exponentially high level.[3] This is owing to the "hook effect" leading to spuriously low/normal levels due to limitations of assay in the setting of phenomenally raised prolactin. Macroadenomas need to be worked up for both functionality (hormone hypersecretion) and evidence of hypopituitarism.[4] This includes testing for thyroid-stimulating hormone (TSH), Free thyroxine (FT4), 8am fasting cortisol, adrenocorticotropic hormone (ACTH), insulin-like growth factor-1 (IGF-1), prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (females) and testosterone (males).[4,5] Definitive treatment for hyperfunctioning tumours is surgical removal. Non-functioning tumours require consideration of surgical removal if there is visual compromise due to chiasmal compression, other neurological compromise, hypopituitarism or a fast-growing mass, as documented from previous magnetic resonance imaging (MRI) records.[5] Secondary adrenal insufficiency and hypothyroidism requires intravenous(I/V) hydrocortisone and thyroxine replacement, with the aim of maintaining haemodynamic stability and keeping (FT4) in the upper quadrant of normal range.[5,6] Correction of secondary adrenal insufficiency may unmask underlying arginine vasopressin deficiency (AVPD). Free water renal clearance is principally regulated by glucocorticosteroids, a process that is retarded in acute adrenal insufficiency. Once deficient glucocorticoids are replaced, there may be abrupt and massive diuresis compounded by revelation of any accompanying AVPD. This can lead to severe hypovolaemia if not managed with intensification of intravenous (IV) fluid replacement and desmopressin.[6]

Pituitary hyperplasia in setting of longstanding untreated primary hypothyroidism needs consideration by repeating MRI pituitary after a period of effective thyroxine

replacement (3 months). Lesion regression over a 3-month period would testify to presence of reversible pituitary hyperplasia. Knowledge of the possibility of this condition can avoid unnecessary surgery. This underscores the importance of measuring both TSH and FT4 when evaluating a pituitary lesion. Typically, majority of large macroadenomas would lead to secondary hypothyroidism having a low FT4 with low or inappropriately normal/marginally high TSH levels. Long-standing untreated primary hypothyroidism leading to pituitary hyperplasia presents biochemically with a clearly raised TSH accompanied by low FT4 levels.[7]

Cushings Syndrome

Hypercortisolism due to Cushing's disease, ectopic Cushing's or adrenal Cushing's requires focus on achieving euglycaemia with insulin and metformin prior to definitive surgical removal of excess ACTH production (Cushing's disease or ectopic Cushing's) or excess cortisol production, independent of ACTH (adrenal Cushings). Blood glucose should be maintained at 140-180mg/dl, which may require insulin infusion. Hypertension management should prioritise the use of angiotensin receptor enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), as these agents would also help to alleviate accompanying hypokalaemia associated with severe hypercortisolism. Spironolactone, a mineralocorticoid receptor antagonist, is a useful adjunct to counter powerful agonistic effect of cortisol on mineralocorticoid receptor, helping to relieve blood pressure, fluid retention and attainment of normokalaemia. Adequate deep venous thrombosis (DVT) prophylaxis, with subcutaneous (SC) heparin (40-60mg SC daily), needs to be instituted given the hyper-coagulopathy associated with hypercortisolism, owing to hyperglycaemia and immobile status commonly seen in these patients.[8] Since hypercortisolism confers a state of immunosuppression resulting from impaired neutrophilic phagocytic activity, timely management of opportunistic infections is vital.[9] To tide the patient over till surgery, agents that reduce production of cortisol or inhibit its action such as ketoconazole, mitotane and metyrapone mifepristone, may be used.[8] The anaesthetic agent etomidate may be desirable to use, owing to its inhibitory effects on steroid synthesis.[10] In the event of failure to identify the source of hypercortisolism, timely bilateral adrenalectomy needs consideration to avoid complications related to long-term use of medication[8,11] and enhanced morbidity and mortality related with inadequately treated hypercortisolism.

Acromegaly

Acromegaly may be associated with hypertension and dysglycaemia requiring optimisation prior to surgical excision (transphenoidal hypophysectomy or craniotomy). Hypertension needs to be managed according to guideline recommendations for the general population, whereby ACE / ARB and calcium channel blocker combinations are useful starting agents.[12] Insulin resistance needs to be countered using metformin. Insulin is often required to achieve preoperative euglycaemia in the setting of severely uncontrolled blood glucose. Obstructive sleep apnoea owing to pharyngeal hypertrophy by excess growth hormone may be overlooked. This needs to be evaluated through history and a validated sleep questionnaire, followed by polysomnography. Preoperative treatment with sandostatin receptor ligand (SRL) would help regression of the swelling, easing intubation for surgery, in addition to application of continuous positive airway pressure (CPAP).[12]

AVPD/ diabetes insipidus

Central diabetes insipidus (CDI), recently re-named AVPD,[13] is a common complication of pituitary surgery, with incidence ranging 10-20%. This incidence can be as high as 60-80% in the case of large tumours, such as craniopharyngiomas.[13] Rates of AVPD are lower with minimally invasive endoscopic pituitary surgery. Postoperative AVPD is transient, with permanent deficiency in minority of cases being 0.5-15%. AVPD is characterised by passing large volumes (>3L/day) of diluted urine (<200mosm/kg). Its occurrence is early, within 24-48 hours post-surgery. It is important to recognise other causes of postoperative polyuria, such as excessive intraoperative and postoperative fluid administration. Another is overzealous use of steroids leading to hyperglycaemia and osmotic diuresis.[14]

AVPD may present in a triphasic manner. The initial polyuric phase results from the inhibition of anti-diuretic hormone (ADH) release due to hypothalamic damage. The second phase is defined by a slow release of ADH by degenerating posterior pituitary, called the syndrome of inappropriate production of ADH (SIADH). Permanent AVPD is due to depletion of posterior pituitary antidiuretic hormones. More commonly, SIADH occurs independently of AVPD carrying with it a significant risk of hyponatraemia, which can be severe.[13,14]

If the patient has significant polyuria (>250mls/hour) with elevated serum sodium and it is difficult to match fluid intake with output, synthetic vasopressin (desmopressin) is indicated. Strict input/output charting is mandatory. Desmopressin should be administered as a single dose, not as regular medication as the AVPD is likely transient. Further dosing should only be administered if symptoms recur or persist. In postoperative settings, subcutaneous administration is preferred; the usual dose being 1ug stat,

then repeat dosing after 12 hours, only when deemed necessary. In patients who do not have an adequate response to subcutaneous preparation, due to an impaired circulation, 2ug desmopressin through (IV) route over 2 minutes is advised. The duration of action for this is 12 hours.[13,14]

If the patient is able to match intake with urine loss (<250mls/hour) and is normonatremic, desmopressin is not required. Inadvertent/overzealous treatment with desmopressin could lead to severe hyponatraemia should the subsequent phase of SIADH develop.[14,15]

SIADH associated with mild to moderate hyponatraemia is successfully managed with free fluid restriction. More severe forms require hypertonic saline.[15] Upon discharge, even if normonatremic, patients should be advised to have a sodium level rechecked should vomiting and headache occur. SIADH, though usually mild and transient, is known to occur by itself, without the classic triad of AVPD-SIADH-AVPD.

Thyroid

Primary Hypothyroidism: Amongst all endocrinopathies, the prevalence of primary thyroid disease ranks second behind diabetes. Symptomatology of primary hypothyroidism is non-specific, ranging from lethargy, cold intolerance, anorexia and body swelling to mental fogginess, mood disorders and decreased cardiac output. Severe untreated hypothyroidism can lead to state of unconsciousness, known as myxedema coma (MC). Delayed gastric emptying may lead to pulmonary aspiration.[16] For anaesthesia induction, FT4, which is a physiologically active hormone, needs to be in the normal range by either introduction (incidentally diagnosed) or escalation of thyroxine in subjects in whom euthyroidism has not been achieved with current dosing. Thyroxine is initiated at 1.6ug/kg/day, orally, aimed at maintaining TSH within normal range (0.4-4.2), requiring 6-8 weeks. In case of urgent surgery, FT4 normalisation, which can be achieved as early as one week with appropriate dosing, can prevent delays in weaning from ventilator ensuing from respiratory muscle weakness.

Severely hypothyroid patients with hypotension and severe neurological compromise, MC, would require IV thyroxine administration. Slow IV infusion of T4 and triiodothyronine (T3) (when available) is the key. The initial dose is 200-400ug IV, followed by daily IV doses of 50-100ug until the patient's condition stabilises and the patient is able to take orally.[17] The lower end of dose would be suitable for thinner individuals, elderly and those predisposed to cardiac complications. IV T3 is given at a dose of 5-20ug daily, then 2.5-10ug every 8 hours. The T3 is continued until patient is clinically stable. Daily monitoring of FT4 and T3 is required, with care to avoid a high T3 and FT4 level, predisposing to arrhythmias.[17] Steroids in stress doses (100mg hydrocortisone every 8 hrs) are required to treat associated underlying adrenal insufficiency owing to autoimmune link between Hashimoto's thyroiditis and adrenalitis. Hypothermia necessitates warm saline administration, bladder lavage and electric blanket. Where parenteral T4 is not available, high doses of T4 tablet via nasogastric (NG) tube has been tried successfully,[17] as well as via the rectal route.[18]

In case of hypothyroidism in the setting of active coronary artery disease, thyroid hormone (TH) administration may worsen coronary artery disease. Some data showed no increase in mortality in hypothyroid subjects undergoing coronary artery bypass grafting who were not euthyroid preoperatively. Cautious TH, with full replacement doses, following correction of cardiac disease is advised.[18]

Primary Hyperthyroidism

An elevated TH production, or release, leads to elevated heart rate, high-output cardiac failure and predisposition to atrial fibrillation, thromboembolism and stroke. Apart from thyroid function tests, namely TSH, FT4 and T3, preoperative blood tests, such as complete blood count (CBC) to look for anaemia, thrombocytopenia as well as glucose, electrolytes, liver and renal function tests are required.[1] Rhabdomyolysis has been reported in severe untreated hyperthyroidism.

Given the direct co-relation between disease severity and intraoperative risk, it is important to assess the extent of thyrotoxicosis preoperatively.[1] Preparation depends upon urgency of surgery. Patients scheduled for elective surgery need to be rendered euthyroid prior to surgery, requiring several weeks. The heart rate is controlled with beta blockers, aiming to keep this <100 beats/minute. In case of emergency surgery, heightened sympathetic response ensuing from hyperthyroidism needs to be controlled by inhibiting both synthesis and secretion of TH. Beta blockade provides adrenergic blockade, through the slowing of HR and decreased potential for arrhythmias. Careful preoperative airway evaluation is essential in case of large goitres that can lead to airway compromise resulting from tracheal compression. A preoperative computed tomography (CT) of the neck and chest to evaluate airway structure may be necessary.

Thyroid storm is the dreaded complication of uncontrolled hyperthyroidism, which can be precipitated by any form of surgical intervention. Marked tachycardia and hyperthermia are the hallmarks of the condition. Altered consciousness and shock may ensue. Oxygenation through

endotracheal intubation, and invasive monitoring, as well as cool IV fluids / cooling blankets / (NG) lavage to address hyperthermia are required. Lugols iodine solution or saturated solution of potassium iodide (SSKI) is useful in addition to anti-thyroid peroxidase inhibitors (thionamides) to rapidly normalise the levels. Lugols is the only agent that blocks TH release, while anti-thyroid peroxidase inhibitors impair hormone production. Of the available thionamides (carbimazole, methimazole and propathiouracil), propathiouracil has the added advantage of inhibiting peripheral conversion of T4 to more active T3. These agents can be given both orally and rectally.[19] Lugols (1-5 drops 3 times daily) needs to be administered an hour after thionamides to prevent iodine content being utilised as substrate for further TH production. Beta blockade is an essential tool to counter dramatic hyperadrenergic response accompanying the thyroid storm owing to its anti-arrhythmic potential.[1,19] Esmolol is quickly titratable short-acting b1-specific blocker better tolerated in asthmatics, chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) (Table 1).

In case beta blockers are contraindicated, guanethidine (inhibitor of norepinephrine release at sympathetic junction) and reserpine (depletes stored catecholamines centrally and peripherally at the adrenal medulla) may be used. Glucocorticoids decrease the peripheral conversion of TH and may be required to treat relative / overt coexisting adrenal insufficiency. Any pre-existing precipitating cause, such as infection, needs to be addressed.

As regards anti-pyretics, acetaminophen is the drug of choice. Asprin needs to be avoided as this can displace thyroxine from thyroxine-binding globulin sites. In extreme situations, direct removal of circulating TH through plasmapharesis, peritoneal dialysis and cholestyramine binding resins (4g 4 times daily) have been utilised with success.[1]

Struma ovari (SO), occurrence of ectopic thyroid tissue in ovary, can be associated with hyperthyroidism (<5-8% cases).[16] SO constitutes 5% of ovarian teratomas, with pelvic and abdominal pain being the common features. In addition to biochemical hyperthyroidism, radioactive iodine uptake (RAI) scan reveals reduced or absent uptake in thyroid gland, as well as positive uptake in the pelvis. Prior to oophorectomy, euthyroidism is achieved using beta blockers, anti-thyroid medication and SSKI. Thionamides and iodine can be safely withdrawn soon after procedure, while beta blockers may require tapering off .[20]

Table-1: Beta blocker use in thyroid storm.

Name of Beta Blocker	Dose of Beta Blocker
Propanalol per oral	60 to 80mg every 4 to 6 hours adjusted for heart rate and blood pressure
Atenolol per oral	25-50mg once daily up to maximum 200mg/day in 2 divided doses
Metoprolol per oral	25-50mg every 8 to 12 hours
Esmolol intravenous	50-100ug/kg/minute

Parathyroid/Calcium

Hypercalcaemia

Hypercalcaemia is medical emergency that may lead to systolic cardiac arrest if not timely addressed. Hypercalcaemia from primary hyperparathyroidism necessitates aggressive IV hydration with normal saline (NS) 0.9%. IV bisphosphonates, such as zoledronic acid 5mg], are concomitantly instituted provided an intact kidney function.[21,22] The aim is to achieve normocalcaemia (upper level of normal approximates 10.5mg/dl), prior to parathyroidectomy. Subcutaneous calcitonin at 4 units/kg every 12 hours is a useful agent to give acutely with bisphosphonates in severe hypercalcaemia, though utility is limited by onset of tachyphylaxis with prolonged calcitonin use.

Denosumab, a fully human monoclonal antibody to receptor activator of nuclear factor kappa B ligand (RANKL) was initially developed as an anti-resorptive agent for osteoporosis, inhibiting both osteoclastic differentiation and maturation. It is approved for other indications, including hypercalcaemia of malignancy (HOM) refractory to bisphosphonate therapy and where persistent renal impairment precludes bisphosphonate use.[21,23] In HOM, denosumab has been used at a dose of 120mg subcutaneously every 4 weeks, with supplementary doses, to achieve steady state levels and rapid lowering of serum calcium levels.[23]

In the setting of hypercalcaemia arising from granulomatous disorders, such as tuberculosis, fungal infection, sarcoidosis and lymphomas, steroids are pivotal in normalising calcium levels in addition to rehydration measures. The macrophages lining the granulomas secrete 1,25 dihydroxy vitamin D. Steroids inhibit alfa hydroxylase enzyme responsible for converting 25 hydroxy D to 1,25 dihydroxy D. They also help through anti-inflammatory action on granulomas.[24,25]

Hypocalcaemia

Severe acute symptomatic hypocalcaemia commonly seen in postradical neck dissection for head and neck cancer requires IV calcium replacement. Asymptomatic hypocalcaemia, with acute decrease of serum corrected calcium to <7.5mg/dl warrants treatment, too. Carpopedal spasm, tetany, seizures, prolonged QT interval are consequences of non-aggressive management. A good IV replacement regimen consists of 1-2g calcium

gluconate/90-180mg elemental calcium, in 50mls 5% dextrose/normal saline, infused over 10-20 minutes. This works for 2-3 hours and should be followed by slow infusion of calcium in persistent hypocalcaemia. The infusion is prepared by adding 11gm calcium gluconate to 1 litre NS run at 50mls/hour, with dose adjustment according to calcium levels monitored every 6-8 hours. The IV calcium is continued until the patient is receiving an effective regimen of oral calcium and vitamin D. For patients with hypoparathyroidism, such a regimen includes calcitriol (activated vitamin D) (0.25-0.5ug/day) and oral calcium (1500-2000mg elemental calcium per day).[26,27] Upon hospital discharge, the subject is counselled to injest extra doses of calcium and double dose of calcitriol in the event of parasthesias and carpopedal spasm while on therapy. More severe symptoms may warrant reinfusion.

In the event of refractory hypocalcaemia, magnesium levels need to be checked since concurrent hypomagnesaemia can lead to hypocalcaemia by inducing parathyroid hormone (PTH) resistance and inhibiting its secretion.[27] In hypomagnesaemia, normal ranges (1.5-2.3mg/dl), 2gm (16mEq) magnesium sulphate is infused as 10% solution over 20 minutes, followed by 1gm (8mEq) in 100mls fluid per hour. Magnesium infusion is continued till magnesium reaches near normal.[27] Persistent hypomagnesaemia, such as that due to ongoing gastrointestinal losses, requires long-term supplementation with oral magnesium 300-400mg daily.

Adrenal / Paraganglioma

Pheochromocytoma is functionally active catecholamine-secreting tumour arising from chromaffin tissue of adrenal medulla. Though a rare tumour, affecting 0.3-0.9% of population, occurrence is life-threatening, demanding intense preoperative management.[1,28] Paragangliomas represent chromaffin tissues elsewhere in the body which, when functionally active, have similar clinical implications as pheochromocytomas. Both elevated serum and urine catecholamines (over twice of the upper limit of normal) are required for diagnosis.[28] Subjects due for the removal of pheochromocytoma / paraganglioma (PPGL) should be prepared at least 2 weeks prior to surgery in order to mitigate dreaded intraoperative hypertensive crisis. Alpha adrenergic blockade needs initiation at least 7 days prior to surgery. This helps normalise blood pressure and expand the contracted intravascular space. This time is required for adequate alpha blockade, to target blood pressure of < 120/80mmHg (seated). Demonstration of orthostatic hypotension represents adequacy of alpha blockade, while not allowing standing BP to drop <90mmHg systolic. This balanced strategy may help to prevent intraoperative hypotension. Longer duration of alpha blockade may be required in cases of recent myocardial infarction, catecholamine-induced cardiomyopathy and refractory hypertension.[1]

Preoperative drug dosing for PPGL has been shown (Table 2). Patients need to be counselled about orthostasis, nasal stuffiness and marked fatigue with alfa-blockade. Selective alpha adrenergic blocking agents (prazosin, terazosin and doxazosin) are preferred over phenoxybenzamine due to their better side-effect profile and low financial cost.[28]

In outpatient settings, blood pressure monitoring should occur twice daily (sitting and standing). It needs to be targetted to low-normal blood pressure for age (average <120/80 mmHg seated; standing ≥90mmHg systolic).

On second to third day of alpha blockade, high-salt diet is recommended (>5000mg daily). This entails enhanced intake of processed food as well additional salt sprinkled over meal-time food, snacks and drinks. This helps to balance orthostasis associated with alpha blockade and catecholamine-induced volume contraction. Enhanced daily fluid intake of approximately 2.5 litres is encouraged. Following adequate alpha blockade, beta blockade is initiated (2-3 days preoperatively). Beta blocker initiation prior to alpha blockade needs to be avoided in order to avoid unopposed alpha stimulation resulting from the blockade of vasodilatory peripheral beta adrenergic receptors. This unopposed alpha stimulation may lead to further blood pressure surges. Care needs to be taken in asthmatics and in subjects with history of congestive cardiac failure. Beta blockers may unmask underlying cardiomyopathy due to chronic catecholamine excess,

Table-2: Preoperative drug regimen for pheochromocytoma and paraganglioma.

Drugs		Initial Doses	Maximum Dose	Initiation
Alfa adrenoreceptor antagonists	Phenoxybenzamine	10 mg twice/day	20-100 mg/day	1-2 weeks prior to surgery
	Prazosin	0.5-1 mg BID	20 mg/day	1-2 weeks prior to surgery
	Doxasosin	2-8 mg/day	16-32 mg/day	1-2 weeks prior to surgery
Beta adrenoreceptor antagonists	Propanolol	10 mg TID/Q1D	120-200 mg/day	After adequate alfa-blockade (to avoid in asthma, bradycardia, shock)
	Atenolol	12.5-25 mg BID	200 mg/day	1-2 weeks prior to surgery
	Metoprolol	25-50 mg BID/TID	150 mg/day	1-2 weeks prior to surgery
CCB	Nicardipine	25-50 mg BID/TID	20 mg TID	1-2 weeks prior to surgery
CA synthesis inhibitor	Metyrosine	500 mg/day	4g/day	1-3 weeks prior to surgery

CCB: Calcium channel blockers, CA: Catecholamine.

precipitating pulmonary oedema. Beta blockers can be titrated to control tachycardia, to target heart rate 60-80 beats/minute. Role of calcium channel blockers is to supplement combined alpha and beta blockade when blood pressure control is inadequate or intolerable side effects develop from this regime.

In the event of intraoperative crisis, IV agents that rapidly normalise BP, such as sodium nitroprusside, phentolamine and nicardipine, are recommended. Cardiac arrhythmias are controlled with the use of lidocaine (50-100mg IV) and / or esmolol.[1]

Sudden post-operative withdrawal of catecholamines may lead to hypotension requiring aggressive fluid replacement (NS 0.9%). Hypoglycaemia from removal of catecholamine load requires IV glucose infusion. Here, glucagon administration as antidote for hypoglycaemia should not be used, as glucagon works by mobilising glucose from glycogen stores in the liver. Glycogen stores in setting of preoperative excess catecholamine are depleted through the process of glycogenolysis. Blood glucose need to be monitored over the next 48 hours. Catecholamine levels should begin normalising in a week's time. Repeat measuring of catecholamines is advised 2-4 weeks before the surgery.[28]

Adrenal Insufficiency

Adrenal insufficiency can be categorised into two main components: primary or secondary. Primary adrenal insufficiency (autoimmune-mediated destruction of adrenals, adrenal tuberculosis, histoplasmosis, metastatic spread to adrenals, being more commonly encountered causes globally) needs to be corrected through glucocorticoid and mineralocorticoid replacement. This often mandates perioperative parenteral hydrocortisone administration (preparation with enough glucocorticoid and mineralocorticoid activity) and IV fluids (NS 0.9%) or full strength dextrose saline (DS) (0.9/5%), if hypoglycaemia prevails. In severe hypoglycaemia, 20% glucose and 0.9% sodium chloride would be more optimal to institute.[1] In case of haemodynamic instability, 100mg immediate dose of hydrocortisone, followed by additional doses every 6-8hours, is required till stability sets in. This is followed by dose tapering corresponding to clinical improvement.[1] The cause of secondary insufficiency is central (involving the pituitary and / or suprasellar structures), associated with minimal mineralocorticoid deficiency. Choice of steroid often leans in favour of dexamethasone owing to latter's impact on the reduction of possible associated cerebral oedema given its more potent glucocorticoid activity. Anaesthetic agent etomidate needs to be avoided as this inhibits steroid synthesis, precipitating adrenal crisis.[29] In case of surgery planned for subject with adrenal insufficiency, on a preoperative stable regimen of steroids, there are protocols for steroid administration based on the nature of surgery (Table 3).

Table-3: Steroid coverage according to intensity of surgical procedure in subjects with stable preoperative steroid regimen.

Intensity/stress of surgery	Dose of Hydrocortisone
Low (inguinal hernia repair/dental procedure)	25mg on day of surgery only
Moderate (revascularization for peripheral arterial disease, open cholecystectomy, colectomy, joint replacement)	50-75mg on day of surgery, tapering over subsequent 2 days to baseline dose
Severe (Coronary artery bypass; Whipple procedure)	100-150mg divided doses for 2-3 days, then taper to usual dose

Steroids may be tapered over the next 1-3 days, then changed to oral stress/maintenance dose (20-30mg hydrocortisone per day), depending on patient's oral tolerance and haemodynamic stability. Treatment of accompanying infection needs to be addressed as failure to do so may render the subject refractory to steroid replacement .[1,29]

Carcinoid Tumours

Carcinoid tumours are well-differentiated gastrointestinal (GI) neuroendocrine tumours located within the GI tract. Symptoms associated with these tumours are linked to excessive production of serotonin and its metabolite urinary 5 hydroxyindolacetic acid. The carcinoid syndrome or crisis occurs in 2-5% patients with carcinoid tumours. The crisis manifests itself as refractory diarrhoea, facial flushing and diaphoresis resulting from the release of tumour mediators. Prior to tumour resection, careful attention to fluid and electrolyte management is required. Parenteral administration of octreotide (300-500ug IV or S/C) helps to reduce the incidence of crisis. Octreotide needs to be continued and tapered slowly if residual carcinoid tissue remains.[1,30]

Bariatric Surgery

Bariatric surgery for complicated obesity necessitates aggressive lifestyle measures in collaboration with a nutritionist to achieve negative caloric balance, physiotherapist to optimise physical activity, as well as weight loss medication (prior to surgery) to achieve best surgical outcomes. There are several weight loss medications available with varying mechanisms of action (Table 4).

Associated diabetes, hypertension, renal dysfunction and dyslipidaemia need to be addressed along with nutritional balance in the postoperative period. In subjects with diabetes on high doses of insulin, blood glucose monitoring needs to continue postoperatively, as there may be a >50% reduction in baseline insulin requirements. This is owing to dramatic reduction in insulin resistance

post-procedure. Dosage of anti-hypertensive medication may also need down-titration.[31]

Nutritional deficiencies need to be sought prior to bariatric surgery, which can be exacerbated following surgery, particularly in those who have undergone extensive procedure, such as gastric bypass.[32,33] These include measurement of serum ferritin, B12, folate and fat-soluble vitamins. There are recommended replacement strategies for the purpose (Table 5).

Table-4: Commonly used anti-obesity medications.

Medication	Dosage	Mechanism of Action
Orlistat	120 mg thrice daily before or with meals	Pancreatic lipase inhibitor- fat malabsorption
Liraglutide	0.6mg once daily, titrated upwards every week- 2 weekly interval to 3mg daily or maximum tolerated dose	Stimulates satiety by acting on satiety centre at hypothalamus; reduces gastric motility (to hold day before surgery-gastric aspiration risk).
Semeglutide	0.25 mg once/week, titrated upwards on 4 weekly interval to 2.4 mg/week or maximum tolerated dose	Stimulates satiety by acting on satiety centre at hypothalamus; reduces gastric motility (to hold 1-2 weeks prior to any surgery- gastric aspiration risk).
Phentermine/ Topimarate	3.75 mg/23 mg/day	Reduces appetite by increasing norepinephrine in hypothalamus; topimarate reduces appetite by acting on GABA receptors
	7.5 mg/46 mg/day	Recommended dose
	15 mg/92 mg/day	Maximum dosage
Naltrexone SR/ Buproprion SR	8/32 mg/day	Induces satiety by acting on adrenergic & dopaminergic neurons in hypothalamus.
	One in morning (AM)-week 1 One in AM, One PM- week 2 Two in AM, One PM-week 3 Two in AM, Two PM-week 4	

Table-5: Recommended vitamin and mineral replacement for bariatric surgery.

Recommended Vitamins and Minerals	
Iron	Present in most over the counter vitamins, like A-Z multivitamins; for additional iron, ferrous sulphate 200mg once/twice daily
Selenium	Present in most over the counter vitamins, like A-Z multivitamins
2 mg Copper (minimum)	Present in most over the counter vitamins, like A-Z multivitamins
Zinc (8-15mg zinc: 1 mg copper) *	Present in most over the counter vitamins; additional zinc to be supplied in 8-15 zinc:1 mg copper ratio *
Folic Acid	5 mg
B12	Intramuscular 1000ug, 3 monthly
Calcium and vitamin D ✓	For vitamin D< 30 mmol/dl, cholecalciferol 50,000 units once per week for 6-8 weeks, then monthly; and 800mg calcium daily; Severe malabsorption: parenteral cholecalciferol 200,000-600,000 units monthly/ q 3 monthly
Vitamins A,E,K (fat soluble)	Sufficient in most available supplements; additional amount required in steatorrhoea
Selenium	Sufficient in most supplements; additional selenium in selenium preparations like Nature's Bounty / ingestion of 2-3 Brazil Nuts
Thiamine ●	Sufficient in multivitamin supplements. If patient has prolonged vomiting, intravenous thiamine (present in Neurobion injection)

* Binding proteins at brush border membrane of gastrointestinal mucosa are activated and bind more avidly to copper than zinc in the presence of supplemental high zinc concentrations. This leads to an impaired absorption of copper to plasma.
✓Pre and post-operative vitamin level >50mmol/l considered ideal.
● In suspected thiamine deficiency, intravenous glucose to be avoided prior to thiamine replacement to prevent Wernicke-Korsakoff syndrome.

Conclusion

Preoperative identification and risk stratification of endocrine disorders is fundamental. Optimisation of the endocrinopathy and its sequelae, geared towards achieving metabolic and physiological control starting well before the procedure is likely to lead to good surgical outcomes. Healthcare centres need to periodically audit their perioperative strategies and surgical outcomes to achieve desirable goals, with minimal morbidity and mortality. Collaboration between anaesthesiologists and endocrinologists is essential in this regard.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

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Author Contribution:
AR: Agreement to be accountable for all aspects of the work.