Anaesthetic management of adrenal tumours presenting with combination of rare syndromes during a pandemic: experience from a tertiary cancer care centre in Northeast India.

Running title: anaesthetic management in adrenal tumour surgery

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Abstract:

Background and Aims: Perioperative management of functional adrenal tumours is resource intensive. Due to the covid 19 pandemic, there has been sizeable delay in preparing and conducting these time sensitive surgeries.Quality of care andresource utilisation may worsen. This retrospective review was aimed at finding if care quality deteriorated due to covid 19 related restrictions, from anaesthetic perspective.

Methods: Three cases of hormone-secreting adrenal tumours operated during a two year period in a tertiary cancer centre in India were retrospectively reviewed.Summary of the demographic profile, tumour characteristics, and the perioperative care were described using tables and analysed in the discussion.

Results: Out of the three cases operated for adrenal gland tumour, pheochromocytoma tumour type with distant metastasis had prolonged hospital stay. One patient developed covid 19 infection in hospital. Cases were adequately managed during the perioperative period and the covid 19 related constraints didn't affect the quality of care.

Conclusion: As in any other major surgery, adhering to a unique checklist, multidisciplinary approach, clear communication, knowledge sharing and establishing a care pathway helps to maintainquality care in high risk cases and at times of crisis.

Key Words: adrenal glands, anesthesia, neoplasm, case management, surgery

Introduction

Anaesthetic management of adrenal gland surgery for hormone secreting tumours is a challenging task. Hormonesecreting adrenal tumours are infrequently met with. Theypresent aseither benign or malignant and are associated with a high risk of perioperative complications. The risk of acute complicationsincreases perioperatively due to catecholamine surge from the tumours during physiological stress, drugs, surgical handling of the tumour, and from sudden decrease in catecholamine level on tumour removal. Mortality due to cardiovascular causes is high inthe perioperative period, with almost half thedeaths in pheochromocytoma occurring during induction of anaesthesia or during surgery for other causes. [1] These can be minimised by careful preoperative evaluation and optimisation, performing minimally invasive surgeries and byproper anaesthetic managementin face of thealtered physiology.[2]Advances in surgical technique and anaesthetic management have reduced the mortality rate to 0 to 3% and chances of complications to 5% to 22%.[3]Perioperative management of adrenal tumours demands intensive resource management and close co-ordination between multiple clinical and non-clinical departments.

The covid 19 pandemic required additional measures on scheduling and planning of these time sensitive surgeries. In this retrospective study, we reviewed three patients with adrenal tumours and associated hormonal syndromes, operated during the pandemic in a tertiary care centre in North East India, with the aim of finding how the pandemic has impacted the delivery of standard care, from the perspective of the anaesthesiologist.

Materials and Methods:

A retrospective study was conductedon three cases of adrenal tumours operated between01/01/2020 to 31/12/2021in a tertiary cancer centre in North-East India.A comprehensive review of the physical case records and the electronic medical record system was done and data was collected and presented in tables. The collected data included the clinical and demographic picture, the radiological, biochemical and pathological characteristics of the tumours, details pertaining to the preoperative, intraoperative and postoperative period and the follow up period. (Table 1, 2)

Preoperative management:

After pre-anaesthetic checkup(PAC), optimisation was done in all three cases with a multidisciplinary approach involvingthe endocrinologist, surgeon, anaesthesiologist and others. Preoperatively, antihypertensive therapy with sequential alpha blocker agent followed by beta blockers and additional antihypertensiveswere started and circulating volume status and nutrition wereoptimised. Active chest physiotherapy and deep breathing exercises were encouraged to minimise hospital stay.

Preoperative care bundle included withholding ACEI (angiotensin converting enzyme inhibitor) and ARB (angiotensin receptor blocker) 24 hours before surgery and continuation of other antihypertensives till morning of surgery. Covid related standard operating procedure (SOP) included preoperative RT-PCR (reverse transcriptase – polymerase chain reaction) test on admission and segregation of elective surgery patients.

Hydrocortisone i.vwas started from the time of operation until allowed orally and thereafter fludrocortisone and hydrocortisone were given.

Anaesthetic management:

For all three cases,difficult airway cart,syringe pumps, antihypertensive drugs like Nitro-glycerine (NTG), labetalol, magnesium sulphate, and vasopressors (vasopressin, noradrenaline) werekept ready.

In addition to standard ASA (American society of Anaesthesiology) monitoring,invasive arterial blood pressure monitoring was done.Peripheral venous access was secured with two wide bore cannulae,epidural catheter was inserted at thoracic 10-11 interspace, and induction of anaesthesia was done with titrated doses of injection propofol I.V.,injection tramadol 100mg I.V. and injection vecuronium0.1 mg per kg I.V.

Ramp position was used and air mattress was madeavailable. Tracheal intubation was done in single attempt in all three casesand haemodynamic response was smooth owing to prior injection of lignocaine 2% 1.5 mg per kg iv. Anaesthesia was maintained with oxygen, nitrous oxide and isoflurane. Neuromuscular blockade was not monitored due to non-availability of neuromuscular monitoring device. Ropivacaine 0.2% 5 ml/h via epidural catheter was started 30 minutes after induction of general anaesthesia.Ultrasound guided right sided internal jugular vein was cannulated post induction and fluid warmers and warming blankets were used.

Epidural catheter was inserted after three attempts in the second patient due to obesity. Intraoperative arterial blood gas analysis was done at regular intervals. Intraoperative events are described in table 3.

Post operative management:

Deep venous thrombosis prophylaxis with stockings was started on day of surgery and low molecular weight heparin (LMWH) was started one day after. Patients were mobilised out of bed on POD 2. Epidural catheter was removed on POD 2 taking into consideration the last dose of LMWH. There were no complications relating to epidural catheterization or vascular access.

The first case developed mild covid infection on post operative day 3 and was managed conservatively.
Case two had a complicated course with excessiveblood loss, long duration of surgery, hypotension requiring inotropic support and hypertension on POD 1 which required nitro-glycerine (NTG) infusion.Epidural infusion was stopped due to hypotension. Post operatively, shewas deliberately kept intubated due to unstable haemodynamics.
She hadbreathing difficulty and decreased oxygenation on POD 2 due to bilateral pleural effusion with hypoalbuminaemia,necessitating the need of NIV (non-invasive ventilation) and B/L intercostal drainage (ICD). She was discharged from ICUon POD7 and stayed in hospital for 15 days. Her final histopathological diagnosis showed pheochromocytoma with high malignant score.She had lung and liver metastasis and later received chemotherapy in the same institute. She had drastic weight loss in follow up and was finally weaned off the antihypertensive.
Case 3 had an uneventful perioperative period.

Discussion:

The anaesthetic management of adrenalectomy is challenging.Various factors influence the perioperative decision making and planning. (Table 4)Rehabilitation is an important aspect of care and should be plannedpreoperatively to begin from the immediate post-operative period. Co-existingcovid 19 infection being relevant in the current scenario considerably increases morbidity and mortality after major surgery.

The most common syndromes associated with adrenocortical tumours in adults are hyperaldosteronism, Cushing's syndrome, less commonly virilization and sometimes combination of any of these syndromes. Cushing's syndrome occurs in 15% of primary adrenal tumours. [4] The occurrence of perioperative complications in adrenal gland surgery varies from 1.7% to 30.7% in the medical literature. [5]

Anaesthetic problems with associated syndromes especially with Cushing's syndrome are mainly faced because of obesity, and associated features of steroid hormone access and end organ dysfunction. (Table 5)

High BMI entailslogistical support. Theatre table and ward bed must be capable of bearing patient weight, and moving equipment like pat slide or pneumatic moving device may be necessary to avoid patient and staff injury. Air mattress helps prevent pressure injury in long surgeries. Surgical equipment and monitoring equipment for large patients will be necessary. Difficult airway, obstructive sleep apnoea, restrictive lung disease and low functional residual capacity (FRC) from obesity make them prone to rapid desaturation.Devices for adequate ramping like Oxford pillow and additional airway equipment may be required. High flow oxygen therapy and video laryngoscope can be used electively to prolong duration of apnoeic oxygenation and reduce the time for laryngoscopy and intubation. Rapid sequence induction is preferred as gastro oesophageal reflux is common.

Patients with Conn's syndrome present with symptoms of hyperaldosteronism, manifesting as systemic hypertension, metabolic alkalosis, hypokalaemia, hypocalcaemia, hypernatremia and associated fatigue, muscle cramps, and skeletal muscle weakness. (Table 6)

Hyperventilation during anaesthesia can aggravate the alkalosis, hypokalaemia and hypocalcaemia and should be avoided.Sevoflurane can cause polyuria and may be avoided. [7]

Out of all the functional tumours, pheochromocytomacan cause more blood loss needing inotropes andhaemodynamic fluctuations and other complications post operatively. 50% of pheochromocytoma patients have severe hypertension refractory to conventional treatment contributing to0.1% of hypertensive population.[8]About 5% to 15% of tumours do not cause hypertension.[10]Paroxysmal or sustained hypertension, tachyarrhythmias, and ectopic discharges in electrocardiograph (ECG) may also be seen in pheochromocytoma. About 30% of these patients have left ventricular dysfunction due to catecholamine induced cardiomyopathy. [12]

Familial causes and associated syndromes (neurofibromatosis 1, multiple endocrine neoplasia type 2, and von Hippel–Lindau syndrome) are present in 25% of pheochromocytomas and these need to be looked for in preassessment.[9] These are associated with additional neurological defects, malignancies and thyroid dysfunction.15-17% of pheochromocytomas develop metastatic disease and in about 11-31% of cases, itpresents as the initial diagnosis. These patients have more adverse complications and bleeding intraoperatively. Currently available therapeutic options are surgical debulking, treatment with radiopharmaceuticals (I-MIBG, Y and Lu-DOTATATE), chemotherapy and targeted therapy.[11]

Undiagnosed pheochromocytoma or inadequately prepared patient may develop hypertensive crisis leading to about 80%mortality.[13]Adequate preoperative preparation with α blockers is traditionally given whichcan reduce perioperative mortality from 45% to 0-3%.Alpha blockade is the mainstay of medical management as it helps to control blood pressure, increase the intravascular volume, prevents hypertensive episodes, reduces myocardial dysfunction and allows desensitization of adrenergic receptors.[14]Invasive haemodynamic monitoring is invariably required ashaemodynamic fluctuations are frequently seen even inadequately prepared patients.(Table 7)

β blocker should never be used before α blockade as unopposed α activity may result in life threatening hypertensive crisis.[17] Adequate pre-operative α-blockade has been proven to reduce the number of peri-operative complications to less than 3%. It is important to start appropriate therapy in all patients with pheochromocytoma and paraganglioma, even if they have normal levels of catecholamines.[16] The morning dose is withheld on the day of the operation tominimize postoperative hypotension.

Either intravenous nitroprusside or phentolamine is effective in management of severe hypertensive crisis, but can cause excessive tachycardia. In such cases labetalol, which is a combined alpha and beta receptor blocker, is more effective.A sudden drop in catecholamine levels at tumour ligation can precipitate hypotension and hypoglycaemia, warranting infusion of two to three litres of crystalloids prior to this.Severe hypotension after tumour removal can be prevented with high sodium diet and fluid intake, as recommended by the endocrine society practice guidelines.[18] The preoperative fluid volume status can be evaluated by the presence of orthostatism, increased heart rate, blood pressure,

increased haematocrit, by ultrasound guided inferior vena cava compressibility index monitoring and use of advanced haemodynamic monitoring such as Flo Trac™ with cardiac output monitoring intraoperatively to assess the need of fluids and vasopressors. Adrenal suppression induces hypotension, decreased cardiac output, hyponatremia, and hypoglycaemia. It is mandatory to control and monitor cortisol level preoperatively. Etomidate must be avoided because it interferes with cortisol synthesis.[19] Apart from the expertise of the surgeon to minimise the handling of the tumour during surgery, intraoperative stimulation of the adrenal gland has the potential risk of unexpected catecholamine surge, resulting in severe hypertension even if the neuroendocrine function of the adrenal gland is normal.[20]A hoard of drugs should be avoided or used with caution in these patients. (Table 8)

Preoperatively, patients are advised to avoid strenuous physical activities, smoking, and alcohol consumption. Use of combined epidural-general anaesthesia has been found to decrease the occurrence of postoperative complications, decrease the stress response and hormonal fluctuations in patients undergoing open surgery for pheochromocytoma.[21]Anaesthesia plane should be deep. Direct sympathomimetics like dopamine or alpha-adrenergic agents like noradrenaline or phenylephrine in higher doses may be required to treat hypotension because of the alpha receptor blockade. Vasopressin may be useful in refractoryhypotension. Labetalol is advantageous for blood pressure control in epinephrine secreting tumours because of its predominant beta action. Dysrhythmias should be treated with appropriate antiarrhythmics like esmolol, amiodarone or adenosine. Blood loss management, temperature regulation, multimodal analgesia should be done as in any other major surgery. Blood sugar must be monitored frequently and for at least next 24hours.

Post-operatively morbidity associated with adrenalectomy has been foundto be as high as 40%, and mortality approximately 2% to 4%.[25]The morbidity is usually due to organ injuries, infection, thromboembolism, or adrenal insufficiency. Common causes of mortality are myocardial infarction, pulmonary embolism, sepsis or worsening of underlying disease.

Intraoperative death, although a rare intraoperative complication, occurs due to severe blood loss, usually from an injury to the inferior vena cava, aorta, or pancreas.[26] Patients' age, comorbidities, BMI, tumour size and pathological diagnosis were found to be independent predictors of post-operative complications.[27]

Perioperative infection with covid 19 is a new dimension to perioperative care, and can have serious consequences. All measures at infection prevention, as stipulated by local authorities and hospital infection control committee should be adhered to, and efforts made to minimise patients physical contact with healthcare system.

Conclusion:

We adhered to a predefined clinical pathway which helped in the successful management of these cases. Most of the recommendations and evidence based guidelines were followed by using a checklist containing the essential points of management.Using similar checklists by surgical teams and in post-operativeunit will be beneficial. Some of the ideal management strategies could not be implemented due to local logistical restraints and covid 19 related additional constraints.

In addition to individual knowledge and skill, a multidisciplinary team approach with knowledge sharing and team meetings helps in the overall management. Establishing regional centres of referral can increase patient load and experience of such centres, improving patient care as well as creating training possibilities of clinicians.

Covid 19 pandemic has put an additional burden for patients visiting health care facilities.However it is essential to continue with medical and surgical care of time sensitive treatments like cancer surgery, albeit at a higher risk of simultaneous covid infection in hospital.

Communication and information to patients, following a 'green pathway' for care of elective patients, as well as education of health care workers can reduce the possibility to certain extent.

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Table 1:Description of clinicodemographic profile of cases, associated syndromes and comorbidities, airway assessment, past history, personal history and their optimisation.

Cases	Airway assessment	Allergy/reflux/smoking/alcohol	Syndromes	Surgery/anaesthesia	Comorbidities	Optimisation
Case 1,27F, 110kg, 150cm (BMI* 49),ASA† II	MPG‡3,TMD§ < 6cm, MO‖ 2 and half fingers, obesity	No allergy, no past history, reflux present, non-smoker, non-alcoholic	Features of Cushing's syndrome, moon facies, hirsutism.no surgery, history of snoring at night.	Nil	Hypertension,H/O intra uterine fetal death three times	Was on spironolactone that was stopped few days before surgery, chest physiotherapy
Case 2, 44F, 150cm (BMI 49), ASA	MPG III, MO 3 fingers, TMD 3 fingers	No allergy, no past h/o surgery or anaesthesia, reflux and acidity present, non-smoker, non-alcoholic	Moon facies, hirsuitism, obesity, history	Nil	hypertension	Prazosin, metoprolol, telmisartan, amlodipin

III			of snoring at night.			e, chest physiotherapy, cardiology and endocrine referral
Case 3, 34F, 150cm (BMI 42) 95 kg ASA II	airway examination normal	none	none	Nil	none	Chest physiotherapy

*BMI-body mass index
†ASA - American society of Anaesthesiology
‡MPG -Mallampatti grade
§TMD- thyromental distance,
‖ MO- mouth opening

Table 2: The different symptoms, provisional and final diagnosis of the tumours, investigations and their associated syndromes.

Case no.	Initial diagnosis (CT abdomen) and syndrome, if any	Special and case specific tests	Symptoms	2DEcho/ ECG/ CXR	Routine blood tests	General examination	Final diagnosis (histopathology)
1	Paraganglioma 8*9*8cm swelling, Cushing's and Conn's syndrome present	S.metanephrine-5.86. 24 hr urine Norepinephrine-5.06. high cortisol, normal renin and high aldosterone. Epinephrine-3.4	Facial puffiness 1year,body ache	EF*-68% ,diastolic dysfunction grade 1,ECG and CXR normal	Normal	Normal	Adrenal adenoma
2	13*8*12cm swelling pheochromocytoma With hepatic and lung metastasis, Cushing's syndrome	High cortisol	Flushing, headache, lower	EF -68% , diastolic dysfunction grade II,concentric left ventricular hypertrop	normal	Bilateral pedal oedema present METS†< 4	Pheochromcoytoma

				hy			
3	Pheochromocytoma 7*8*6cm.no syndrome present	24hr urine metanephrine 47ug/24h. Cortisol 5.21ug/dl. Rennin act-18.3uIU/ml Prolactin-42 (h)ng/ml Aldosterone-4ng/dl	Paroxysmal headache,dizziness 2 years, palpitation	EF -60%, rest normal, ECG normal	normal	Nothing significant	Adrenal cortical adenocarcinoma

* EF – ejection fraction
†MET - Metabolic equivalent

Table 3:The duration of surgery, total intravenous fluids and blood products transfused, blood loss, urine output and tracheal extubation status and post-operative complications.

Cases	Duration of surgery	Blood loss	IV* fluid	Urine output	Blood products	Events	Extubation	Use of inotropes	Post operative complications
Case 1	4 h	650mL	3L	150mL	1unit PRBC†, 250mL	Persistent tachycardia	extubated	none	Poor breathing effort, need of NIV‡, post operative covid infection
Case 2	5h	4 L	5.7 L	800ml	4 PRBC, 4 FFP§ and 4 platelets	Noradrenaline up to 10ml/h	Not extubated	Continued till post op day 2	Post op hypertensionpod1, pleural effusion B/LICDǁ, need of NIV
Case 3	4.5h	1 L	4L	150ml	1unit PRBC 250ml	uneventful	extubated	none	uneventful

*IV - Intravenous, †PRBC - packed red blood cells, ‡ NIV – non invasive ventilation, §FFP - fresh frozen plasma, ǁICD – intercostal drain

Table 4:Various factors influencing the perioperative decision making and planning

Factors affecting perioperative decision making
Patient related Age, frailty, body mass index, comorbidities
Tumour related

Type, size, grade, left or right sided, extra adrenal, hormone secreting
Surgical related Surgical skill, unilateral or bilateral surgery, patient positioning, approach (open or laparoscopic), expected blood loss, duration of surgery
Anaesthesia related Airway, vascular access, possible haemodynamic crisis, likely post-operative complications, pain management, post-operative nausea and vomiting
Additional issues Nosocomial infection prevention, COVID 19 protocols
Rehabilitation

Table 5: Clinical features and perioperative considerations in Cushing's syndrome.

Cushing's syndrome	
Clinical feature	*Perioperative consideration*
High BMI	Appropriate theatre table, equipment for moving patients, anaesthetic and surgical equipment appropriate for large patients
Airway, lung disease and oxygenation	Difficult airway, sleep apnoea syndrome, restrictive lung disease, rapid desaturation with apnoea
Acid reflux disorder	Aspiration prophylaxis
Insulin resistance, dyslipidaemia	Insulin therapy, lipid lowering agents
Immune dysfunction	Infection prevention
Osteoporosis, fragile skin	Prevention of fractures and skin breaks/injury during positioning for surgery
Proximal myopathy	Increased sensitivity to muscle relaxants
End organ damage to heart, brain, kidney, eyes from hypertension, dyslipidaemia, high blood sugar	Focused clinical review for detection. ECG, fundoscopy, renal function test, echocardiography as baseline tests, preoperative optimisation where possible.
Deep venous thrombosis	DVT prophylaxis-low molecular weight heparin (LMWH), stocking, caff compression device, early mobilisation

Table 6:Metabolic defects and perioperative considerations in Conn's syndrome.

Conn's syndrome	
Metabolic defect	*Perioperative consideration*
Hypokalaemia	Prolonged action of muscle relaxants, reduced physiological response to hypovolaemia, supraventricular and ventricular arrhythmias
Alkalosis, hypocalcaemia	Worsened my mechanical ventilation with hyperventilation, sevoflurane induced polyuria
Hypernatremia and associated skeletal muscle weakness	Avoid high sodium intravenous fluid

Table 7:The antihypertensive drugs used in pheochromocytoma with relative merits and uses.

Antihypertensives in pheochromocytoma		
Drug name	*Drug class*	*Merits/demerits*
Phenoxybenzamine	$\alpha_1+\alpha_2$ blocker	Preoperative therapy, long acting drug, can produce postural hypotension, tachycardia
Phentolamine	$\alpha_1+\alpha_2$ blocker	Very short acting drug, intravenous use in

		hypertensive crisis
prazosin terazosin doxazosin	Selective(alpha) α blocker	Preoperative therapy, short acting drug, does not produce tachycardia, can produce postural hypotension
Metoprolol Atenolol	Selective(beta) β_1 blocker	Started after α blockers to control blood pressure, tachycardia. Metoprolol can be used intraoperative for tachycardia control
Propranolol	$\beta_1+\beta_2$ blocker	Started after α blockers to control blood pressure, tachycardia. Not for intraoperative use
Esmolol	β_1 blocker	Ultra-short acting drug, for intraoperative use
Labetalol, carvedilol	α+β blocker	Second choice drug to α blockers for preoperative use, more β than α blockade (1:7), useful in intraoperative hypertension
Amlodipine, nifedipine, nicardipine, verapamil	Calcium channel blocker	Add on to adrenoceptor blockers to reduce their dose and side effects, while achieving blood pressure control
Metyrosine	Catecholamine synthesis blocker	In metastatic tumours, inoperable patients, to control blood pressure
Nitroprusside, Nitro-glycerine	Vasodilators	For intravenous use in hypertensive crisis

Table 8: List of drugs to be avoided and its rationale.

Drugs to be avoided		
Drug name	*Class*	*Reason*
Propranolol, atenolol, Metoprolol	β blocker	Not to be started before adequate α blockade, can cause severe hypertension
Glucagon, steroids, vasopressin, histamine, angiotensin II		Stimulate production of catecholamine.
Tyramine containing food- banana, cheese, avocado, wine etc		Cheese reaction-catecholamine release from storage vesicles
Phentermine, Methamphetamine, phenylethylamine	Drugs for obesity	sympathomimetics
Ephedrine, pseudoephedrine, phenylpropanolamine	Nasal decongestant	sympathomimetic
Amitriptyline, Nortriptyline, Duloxetine, Venlafaxine	Tricyclic antidepressants	Catecholamine reuptake inhibitors
Cocaine		Catecholamine reuptake inhibitors
Selegiline, Linezolid	Monoamine oxidase inhibitor effect	Inhibits metabolism of catecholamine
Metoclopramide, chlorpromazine, prochlorperazine	Antiemetic, antipsychotic	Dopamine receptor antagonists, decrease dopaminergic inhibition on catecholamine synthesis
Succinylcholine, atracurium, rocuronium, mivacurium	Neuromuscular blockers	Ganglionic stimulator, histamine release