



Laparoscopic Bilateral Adrenalectomy in a Patient of Cushing Disease due to Pituitary Microadenoma: a Challenge for the Anaesthesiologist

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Introduction

Cushing's syndrome has a multi-factorial aetiology. Administration of exogenous steroids in oral formulations, injected or inhaled forms can cause development of Cushing's syndrome. Endogenous causes may be ACTH dependent (80% of the cases) or independent (20% of the cases). ACTH overproduction may be of pituitary origin (85% cases) or result from ectopic tumor secretion (15% cases). The term Cushing's disease is specifically applied to ACTH-secreting pituitary tumors. ACTH independent causes are mainly due to benign (60%) or malignant (40%) adrenal tumors. Several studies have shown the association of Cushing's Syndrome with pheochromocytoma [1,2] sarcoidosis [3], pancreatic acinar cell carcinoma [4], pre-eclamptic findings [5], malignant gastrinoma [6], bronchial carcinoid lung tumour [7], pancreatic neuroendocrine tumour [8], Hippel-Lindau disease [8] or mesenteric neuroendocrine carcinoma [9]. Our patient had pituitary micro-adenoma or Cushing's disease with none of the above associations. Trans sphenoidal surgery is the first line treatment of Cushing's disease, but it was not possible in our patient.

Case Report

An 18 yrs old lady was referred to the endocrinology department with suspected Cushing's syndrome on the basis of one year history of rapid weight gain, swelling of face, hirsutism, broad pink striae, headache, visual disturbances and five months history of amenorrhea (menarche at 12 yrs). Her birth history and developmental history was normal. She had no history of prolonged intake of corticosteroid. On examination her body weight was 59.1 kg (>97th percentile), height 108 cm (<3rd percentile) and BMI 42.44kg/m² (morbid obese). Broad pink striae (>1 cm) over shoulder, abdomen and back were present. Acanthosis, cervical pad of fat and pigmentation over knuckle were present. On general survey P⁰ Cy⁰O⁺ (none pitting) J⁰. Tanner's stage was B₄P₁. BP was 140/90 and patient was on tab Amlodipine (10 mg) OD and tab spironolactone (25 mg) OD. She was taking tab ketoconazole 400mg/day, but it failed to give any improvement. On confrontation perimetry left eye was within normal limit but right eye showed loss of field in cephalad and outward direction. Patient had mild proximal myopathy. Other systems were normal. She was admitted for further investigations, including a high-dose dexamethasone suppression test, a corticotrophin-releasing hormone

(CRH) stimulation test and imaging studies. Basal cortisol level was 19.1 mcg/dl. High dose dexamethasone suppression test was 7.5 mcg/dl i.e. >50% suppression (as basal cortisol level was 18.8 mcg/dl before the dexamethasone administration). Her 24 hour urinary cortisol level was 1532.72mcg/day (Ref range 58 to 403 mcg/day), morning plasma ACTH was 52.87 pg/ml (Ref range 7.2 to 63.3 pg/ml). The results of these tests confirmed a diagnosis of Cushing's disease due to microadenomas of the pituitary gland (in M.R.I. nodular hypointensity 4x6 mm seen in right side of pituitary gland). Patient was unable to do inferior petrosal sinus sampling (IPSS) because of the high cost of the test (Rs.6000 in our settings). The pituitary pathology was not deemed operable, as there were multiple small adenomas present and patient wanted to preserve her fertility. As a result, she was booked for laparoscopic bilateral adrenalectomy in department of urology.

Preoperative Assessment

In the preoperative checkup she had typical cushinoid features but systematically she was doing well. Her blood pressure was 130/90. Blood glucose and electrolyte levels were within normal limits. Airway examination revealed restricted mouth opening, malampati grade 3, normal mandible. Neck movements are normal, but she had short neck with buffalo hump. She was most comfortable lying in a semi-recumbent position at night and had history of snoring when asleep, with occasional spells of apnoea. So we anticipated that it might be a difficult ventilation and intubation. Examination of other systems was normal. The preoperative treatment included ketoconazole 400 mg per day, which was started 3 months before the surgery, and continued until the morning of the intervention day and tab calcium and vitamin D3 and zoludronic acid. For hypertension she was taking tab amlodipine 10 mg OD and spironolactone 25 mg OD.

Day of Operation

On the morning of surgery she was taken to the OT. All standard monitors (NIBP, pulse oxymeter, ECG) were attached. Two intravenous cannulas of 18 G were put in place. She was premedicated with inj glycopyrrolate (0.2 mg), inj fentanyl (100 mcg) inj metoclopramide (10 mg) and inj clonidine (45 mcg). After 3 minutes of preoxygenation, she was induced with inj propofol @ dose of 2mg/kg body weight. Once it was confirmed that bag-mask ventilation was possible inj succinylcholine was given at a dose of 1mg/kg body weight. She was intubated with 7.00 mm ID cuffed endotracheal tube uneventfully which was fixed at 17 cm at the angle of mouth. After induction an arterial catheter in right radial artery for invasive blood pressure monitoring and doing serial ABG was inserted. Right internal jugular vein was also cannulated. Anesthesia was maintained with 3:5 O₂:N₂O and titrated dose of isoflurane. Muscle relaxation was achieved by 0.3 mg/kg inj atracurium bolus followed by 0.1mg/kg/hr atracurium infusion. The patient received a bolus of 100 of hydrocortisone and 8 mg dexamethasone soon after induction. Further monitoring included end-tidal CO₂ and temperature monitoring. Inj fentanyl (25 mcg) was given 30 minutes interval as analgesia.

Her haemodynamic parameters were maintained throughout the OT, with mean arterial BP ranging from 65-90 mm of Hg. Blood glucose level at induction was 80 mg/dl and after extubation it was 200 mg/dl. No insulin was administered intra-operatively. At first patient was positioned in left lateral position for accessing right adrenal first,

and then right lateral position for left adrenal gland. Every effort was made to ensure that pressure points were adequately padded, and her eyes were taped closed.

Surgery was largely uneventful. Access to the adrenal glands was gained laparoscopically via a lateral transabdominal approach, using CO₂ to insufflate the abdomen and keeping intra-abdominal pressures below 15 mmHg.

We gave 100 mg inj hydrocortisone after ligation of left renal vein.

At the end of surgery isoflurane was discontinued and muscle paralysis was reversed with inj neostigmine 2.5 mg and inj glycopyrrrolate 0.5 mg. Patient was extubated in semi-recumbent position when she was full awake and maintained her own airway adequately in room air. She was transferred to the recovery room for further management and did very well, remaining there for two days. Antihypertensive medication and inj hydrocortisone were continued throughout the post operative period as per advice given by endocrinologists. Monitoring of ACTH level and pituitary MRI are recommended 3-6 months after surgery and regularly thereafter.

Discussion

Glucocorticoids regulate protein, fat, carbohydrate and nucleic acid metabolism. Increased production of cortisol results in Cushing's Syndrome which is characterized by [10,11]:

- Obesity: obesity with centripetal fat deposition (face, supra-clavicular and dorso-cervical fat pads), facial plethora, moon facies, buffalo-hump
- Signs of protein wasting: thin skin, abdominal purple to red and wide cutaneous striae (abdomen, flanks, breasts, hips, axillae), easy bruising, slow healing, muscle wasting (lower limbs muscle atrophy)
- Bone wasting leading to osteoporosis (possibly leading to fractures)
- High blood pressure
- Impaired immune defense mechanisms with increased rate of infections
- Gonadal dysfunction and hyperandrogenism: hirsutism (more frequently on the face), menstrual irregularity (oligoamenorrhea, amenorrhea)
- Mild to severe psychic disturbances (anxiety, depression, irritability.)

Our patient could not afford IPSS and the plasma level of ACTH was within normal limits. So most probably her disease was not from pituitary origin. The young lady was only 18 yrs old and she wanted to preserve her fertility. Though a microadenoma was seen in pituitary, endocrinologists were referred the patient to urology for doing b/l adrenalectomy.

Multidisciplinary teams that involve an endocrinologist, neurosurgeon, general surgeon or urologist and anesthesiologist can guarantee the effective diagnosis and management of CS and disease. Patients with Cushing's syndrome and Cushing's disease present a multitude of challenges for the anesthesiologist.

Pre-operative optimization and preparation of the patient

Medical treatments aim at decreasing synthesis and secretion of cortisol, blocking glucocorticoid receptors, or inhibiting ACTH secretion. Medical treatment only controls hypercortisolism but can't cure it. Various drugs are available for this measure like steroidogenesis inhibitors [12] (mitotane, ketoconazole, metyrapone, etomidate), glucocorticoid receptor antagonist (mifepristone), ACTH-lowering agent (cabergoline), temozolamide. Our patient was receiving ketoconazole. But medical therapy failed to show any clinical and biochemical improvement and some adverse reaction like gastric intolerance and nausea were manifested.

These patients are generally hypervolemic and hypertensive, often receiving chronic anti-hypertensives. All anti-hypertensives should continue till morning of surgery except angiotensin converting enzyme inhibitors and angiotensin receptor blockers which are associated with severe hypotension with anaesthetic induction. These patients may also present with hypokalemic metabolic acidosis. Pre-operative treatment with spironolactone reduces potassium loss.

Our patient was receiving spironolactone and her electrolyte levels were within normal limits.

Hyperglycaemia is another concern for these patients. Cortisol promotes breakdown of protein and neoglucogenesis in the liver. It also antagonises the effects of insulin. These actions help in maintaining normal blood glucose levels during fasting state. But, excess circulating cortisol results in glucose intolerance, which ultimately may result in onset of type II diabetes. Hyperglycaemia is associated with decreased wound healing, increased morbidity and mortality leading to increased hospital stay [13,14,15]. Oral hypoglycaemic agents are avoided before surgery. Our patient was maintained with regular insulin. Plasma glucose was checked hourly and we were prepared to manage any eventuality- both for hyper-glycaemia and hypoglycaemia.

These groups of patients are generally obese, which is of prime concern for anesthesiologists. Our patient was morbidly obese with a B.M.I. of 42 kg/m². Obesity is associated with hypertension, dyslipidaemia, ischaemic heart disease, diabetes mellitus, osteoarthritis, liver disease, and obstructive sleep apnea [16]. Therefore, a detailed cardiovascular history and examination is essential, and depending on these findings, further investigation may be required. Obesity causes decreased pulmonary compliance which contributes in reduction of functional residual capacity, atelectasis, ventilation/perfusion mismatch and intra-pulmonary shunt, ultimately leading to hypoxemia and rapid desaturation. Intra-venous cannulation of these patients also is sometimes problematic. In our patient, though peripheral i.v. line was easily secured central venous cannulation was a bit challenging. Mask ventilation and intubation of these patients may be difficult. Prediction of difficult airway is very important in pre-anaesthetic check up. Several parameters such as Mallampati score, mouth opening, neck extension, thyromental and sternalmental distances, and Wilson score are used to predict difficult intubation. Hence, pre-operative deep sedation of these patients is avoided.

Intra-operative considerations

Patients are adequately preoxygenated since various respiratory complications may arise. There is no specific induction agent of choice, although ketamine is avoided due to its sympathetic effects. Our patient was induced with thiopentone sodium. Fentanyl, sufentanyl

and remifentanyl are the commonly used opioids. Remi fentanyl is preferred due to its ultra-short effect contributing in reduced respiratory depression and enhanced recovery. We used fentanyl due to unavailability of others. Obesity also increases the risk of gastric aspiration, so rapid sequence induction was done. Choice of antibiotics and their dose is an area of concern since these patients may have myopathy, causing delayed recovery.

Hypercortisol levels have immunosuppression and strong anti-inflammatory effect [17]. This inhibits pain, swelling, cellular immunity, wound healing and repair. Hence, all the procedures like placement of epidural catheter, arterial lines and central venous catheter should be done maintaining strict aseptic guidelines. Prophylactic antibiotics should be administered to prevent any opportunistic infections. All these points were carefully followed in our patient.

Thin skin, easy bruiseability, increased body weight and osteoporosis make these patients prone to developing pressure sores, soft tissue and bony injuries and nerve injuries. All the pressure points should be adequately cushioned.

Obesity, absence of normal physical activity, hypertension and hypercoagulable state makes these patients prone to develop deep vein thrombosis. Prolonged duration of surgery is also an independent risk factor. Various modalities like unfractionated heparin, low molecular weight heparin and lower extremity compression devices are available for prevention. Early post-operative mobilization is also helpful. We applied lower extremity compression device for both intra-operative and post-operative periods.

Laparoscopic procedure in these patients aggravates the already compromised respiratory functions due to obesity. Ventilation should be adjusted in guidance with capnography. Laparoscopy is also associated with hemodynamic changes. Adequate preloading with fluids must be done.

Hypothermia is a concern in prolonged surgery. The temperature of operation theatre was maintained between 27-28°C. The fluids administered were optimally warmed and the patient was adequately covered.

Endogenous secretion of cortisol rises in response to major surgery and this rise is directly proportional to the duration and extent of surgery. Increased cortisol levels prevent stress induced shock and hypotension. Hence, glucocorticoid replacement should be done intra-operatively and continued post-operatively.

These patients are extubated only when the patients are awake, fully reversed from muscle paralysis and taking spontaneous respiration regularly and is hemodynamically stable.

Post-operative care

Post-operatively the patients should be monitored closely to prevent respiratory complications. Pain must be relieved adequately by multi-modal approach, if necessary. Early mobilization and respiratory exercises should be advocated. Glucocorticoid replacement should be done in consultation with an endocrinologist. Routine cortisol level, blood sugar and electrolytes levels should be assessed [18].

Another life-threatening complication of total bilateral adrenalectomy is Nelson's disease, but it develops after almost 15 yrs. Incidence of the disease is 8-29%. In literature bilateral adrenalectomy

is said to carry an acceptable risk but follow up should include awareness of it [19].

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