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The Anesthetic Challenges of Bilateral Adrenalectomy in a Patient with Recurrent Cushing's Disease

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ABSTRACT

Bilateral synchronous adrenalectomy (BA) is an infrequently done, yet an effective and a challenging procedure for refractory Cushing's disease.

A 21-years old female with persistent hypercortisolemia following 2 trans-sphenoidal hypophysectomies for Cushing's disease was referred for BA. Her strong desire to bear children precluded radiotherapy and long-term medical management as treatment options over BA to control hypercortisolemia.

The decision process leading to surgery, pre-operative pre-habilitation, anesthetic considerations, the challenges of management of acute withdrawal of cortisol following BA, and the peri-operative course will be discussed.

KEYWORDS

Pituitary microadenoma; Cushing's disease; Bilateral laparoscopic adrenalectomy

INTRODUCTION

Cushing's disease, first described by Nikolai Itsenko and Harvery Cushing is a clinical condition with hypercortisolism (central obesity, hirsutism, acne, menstrual dysfunction, emotional lability, hypertension, glucose intolerance and osteoporosis) resulting due to an ACTH secreting pituitary microadenoma [1-3].

Hypercortisolism with active Cushing's disease predisposes to high mortality and morbidity [1,4]. Cushing's disease is commonly managed with Trans-sphenoidal adenectomy (TSA), but a recurrence rate of 13% at ten years has been reported [1]. If there is a recurrence or in persistent disease following an unsuccessful initial surgery, a repeat TSA, medical management, or radiotherapy are commonly considered.

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Synchronous bilateral adrenalectomy (BA) in the management of Cushing's disease is a rarely undertaken challenging surgery as BA itself carries multiple perioperative risks [1]. Medical, surgical, and anaesthetic concerns associated with the surgery should be considered and patient should be well optimized for a successful surgical outcome in BA.

CASE REPORT

A 21-years old married Sri Lankan lady was evaluated for weight gain, oligomenorrhea and hirsutism. At the presentation, she had had typical Cushingoid features. Non-suppressed overnight and low dose dexamethasone suppression test (LDDST), an elevated ACTH level and a 9.6 mm × 6.7 mm lesion in the pituitary fossa in MRI brain had confirmed the diagnosis of Cushing's Disease (CD). She had undergone a transsphenoidal resection of a pituitary microadenoma in May 2018 which resulted in biochemical remission (morning cortisol 105 nmol/L on post op day 7; early post-operative morning cortisol <138 nmol/L is considered as remission [5]. Histology had indicated an ACTH secreting microadenoma with a Ki-67 of 10%. Follow-up at six months indicated a recovery of her hypothalamic-pituitary-adrenal axis. At post-operative 1 year, MRI pituitary showed structural recurrence with the encroachment of the left cavernous sinus and there was evidence of biochemical recurrence with non-suppression of cortisol (180 nmol/L) on LDDST. She had undergone a second transsphenoidal surgery for the recurrence in August 2019. Histology again confirmed ACTH secreting adenomatous tissue, with no evidence of malignancy. A high ACTH levels (174 pg/mL: normal range: 15 pg/mL - 75 pg/mL), non-suppressed cortisol levels on overnight dexamethasone suppression (410 nmol/L) and on LDDST (356 nmol/L) post-operatively were noted during the immediate post-operative period, indicating persistent disease [5]. MRI pituitary performed 4 months postoperatively demonstrated residual tumour, with further encroachment of the left cavernous sinus and carotid artery. In the background of a surgically unresectable tumour, second line treatment options were discussed. She had strong fertility wishes and opted for best possible chance for natural conception with a functional hypothalamic-pituitary-ovarian (HPO) axis. After an extensive discussion at the multi-disciplinary meeting and with the patient, bilateral adrenalectomy was planned in lieu of radiotherapy, which would have effectively affected her chances of pregnancy by its effects on HPO axis. Medical treatment with somatostatin analogues were not preferred considering the time taken for normalization of cortisol axis and its success rates.

Six months before the current admission, she was diagnosed with diabetes mellitus and found to have secondary hypothyroidism. Her medications included metformin 500 mg twice daily and thyroxine 125 mcg daily.

The patient had Cushingoid features. She weighed 75 kg, was 150 cm in height and her BMI = 33.4 kg/m^2. She had good exercise tolerance. She had a Mallampatti class 2 airway, with a thyro-mental distance of 6.5 cm.

Laboratory investigations were as follows; Hb 13.8 g/dl, WBC 9.85 × 103/l, Platelet count 278 × 103/L, Na+ 141 mmol/l, K+ 3.9 mmol/l, INR 0.98, HBA1C 6%, Fasting blood sugar 108 g/dL, TSH 1.01 u/L (0.4 - 4), free T4 10.3 pmol/L (7.9 - 14), 24 hours urine free cortisol level 462.6 nmol/day (55 - 248). FSH, LH, renal function tests and liver function test results were within normal ranges. Her 2D echocardiogram was normal, with an ejection fraction of 66%. ECG and lung function tests were normal. Pre-operative arterial blood gas on room air was as follows; pH 7.38, $PaCO_2$ 41 mmHg, PaO_2 98 mmHg, HCO_3 23.6 mmol/l, BE 2.1 mmol/l. The pre-operative ultrasound showed bilateral adrenal hyperplasia.

The departments of surgery, endocrinology and anaesthesia were collaboratively involved in preparing

this patient for surgery. Close attention was given to pulmonary pre-habilitation, blood pressure and blood sugar control, preventions of infection and deep vein thrombosis (DVT). Considering the perioperative mortality and morbidity associated with high cortisol levels, decision was taken to use adrenocorticolytic treatment to reduce the cortisol burden prior to the surgery. As metyrapone or ketoconazole was not available in the government sector hospitals, we used fluconazole as an adrenocorticolytic agent in our patient with a dose of 400 mg/day for 6 weeks prior to the surgery which dropped the cortisol burden from an average cortisol levels (from a cortisol day curve) of 856 nmol/L to 370 nmol/L.

Pre-operatively an epidural catheter at T9 level - 10 level, central venous catheter in the right internal jugular vein, a left radial arterial catheter, and AAGBI standard monitors were applied.

Prior to induction, hydrocortisone 200 mg IV loading dose followed by an infusion at 3 mg/h started via the central line. Anaesthesia was induced with propofol 160 mg, fentanyl 100 mcg and atracurium 50 mg and maintained with isoflurane in oxygen. She was intubated with a 7.5 mm ET tube and received morphine IV in aliquots. Antibiotic prophylaxis consisted of 4.5 g piperacillin-tazobactam, 500 mg metronidazole and 80 mg gentamicin.

0.9% saline infusion was used as maintenance replacement. More than 65 mmHg mean arterial pressure and at least 0.5 ml/kg/h of urine output were maintained. Hourly blood sugar and ABG measurements were performed.

The patient was placed supine, and the operating table was tilted left or right as required for bilateral Laparoscopic Adrenalectomy. Adrenalectomy was performed via anterior approach. Patient positioned in the left and right lateral positions consecutively to access each gland as it is the preferred route in our surgical unit. Veress needle technique with 5 ports on each side was employed. Adrenal glands with surrounding perinephric fat dissected with ultrasonic shears and bipolar diathermy. Adrenal glands were removed as a whole without any fragmentation and the specimens were retrieved separately in bags. Removed gland sizes measured: Left side: 6.2 cm × 1.8 cm × 2.1 cm and Right side: 6 cm × 4.5 cm × 0.5 cm.

During dissection of the right adrenal gland, there was a period of hypertension to a 180 mmHg systolic pressure, which was managed with a bolus of epidural bupivacaine and an increased dose of inhalation agent. After resection of the left adrenal gland, the systolic blood pressure declined to 80 mmHg, necessitating an adrenaline infusion at 0.05 mcg/kg/m - 0.15 mcg/kg/m to restore blood pressure. Hydrocortisone 50 mg IV bolus was administered, and the infusion was increased to 5 mg/h.

The total duration of surgery was 320 minutes. Intra-operative blood loss was less than 200 ml, and a total of 2L of 0.9% saline was administered. Total urine output was 900 ml. Capillary blood sugar levels remained between 120 mg/dl - 160 mg/dl, and serum potassium remained normal throughout the surgery. At the conclusion of the surgery, her core temperature was 34.8°C. She was extubated and transferred to the ICU for postoperative care. IV hydrocortisone infusion was continued for three days and tapered down to 2 mg/hr before being converted to IV 50 mg 6 hourly dose on POD 3. Enoxaparin 60 mg SC daily was commenced 6 hours after the surgery, and IV antibiotics were continued. Analgesia was maintained with an epidural infusion of 0.1% bupivacaine and fentanyl.

The patient was mobilized in a graduated manner. On the postoperative day (POD) 3, she developed respiratory distress and a fall in PaO_2 due to bilateral basal pulmonary atelectasis. Pulmonary embolism was excluded from a CT pulmonary angiogram. This situation was managed with non-invasive CPAP for 48 hours. Antibiotics were

changed to IV meropenem and teicoplanin. She was discharged from the ICU on POD 6 and was discharged from the hospital on POD 10 on replacement oral hydrocortisone and fludrocortisone therapy. Cortisol levels performed on POD 14 after withholding oral hydrocortisone for 12 hours was less than 20 nmol/l, indicating complete metabolic resolution following surgery. Post-operative ACTH was 210 pg/mL (15-75). Histology showed bilateral adrenal hyperplasia. The patient is metabolically stable on replacement therapy when reviewed at the two-month follow-up visit.

DISCUSSION

Out of the treatment options looked in this patient with the view of the two failed pituitary operations and the more extensive local spread, Radiation therapy seemed to offer the best choice to control local extension into the left cavernous sinus and carotid artery, but the fact of that associates with a considerable risk of hypopituitarism [1]. The patient's strong desire to bear children precluded radiation therapy. The options remaining to her were noted to be aggressive medical management with or without a bilateral Adrenalectomy. New medications such as metyrapone, ketoconazole, mifepristone, pasireotide are advanced medical therapies [1]. They are used to control localized disease where complete tumour eradication has not been possible or where the candidate is unsuitable for surgery or radiation. Medical therapy is also used as a presurgical treatment, particularly for severe disease or post-surgical management in failure or incomplete surgical resection or bridging therapy for radiotherapy [1,4]. However, considering the duration it would take for normalization of hypercortisolism to suit a pregnancy, the success rates of the medications and safety profile in pregnancy, above medications were not considered as the therapeutic option for this patient as the second line management option. Therefore, next best option of bilateral adrenalectomy was selected for this patient for control of hypercortisolism.

Literature indicate that CD preoperatively treated with adrenal-directed medications might have a lower risk of intraoperative bleeding, thus a better surgical outcome [6]. Ketoconazole and metyrapone are steroidogenesis inhibitors and have a rapid action compared to other agents like glucocorticoid receptor antagonists, mifepristone. They are being commonly used as preoperative medical therapy. Of the other ACTH lowering drugs, cabergoline is a dopamine agonist and pasireotide, a somatostatin analogue, is known to result in disease remission in a subgroup of patients with CD [1,4]. However, due to the unavailability of above drugs, fluconazole was used for this purpose. Fluconazole, an azole antifungal, inhibits 11B-hydroxylase and 17-hydroxylase activity in human adrenocortical cells in vitro studies. However, it has shown at least 40% less potent compared to ketoconazole [7]. Literature is now emerging on the usefulness of fluconazole as an adrenal steroidogenesis inhibitor, especially where conventional medications are not available. Our patient has also responded well to fluconazole in bringing down the average cortisol levels to an acceptable range prior to adrenalectomy to reduce associated with mortality and morbidity [7].

BA will lead to complete control of CD in 97% of patients but has higher perioperative morbidity and mortality compared to medical treatment [1]. The risk of acute adrenal insufficiency intra and postoperatively evident to have a disastrous outcome, including hemodynamic collapse [1].

The laparoscopic approach, which is the surgical method of choice in the unit, offers a better outcome than open laparotomy in terms of morbidity, mortality, recovery time, length of hospital stays and perioperative complications. Compared to open laparotomy, Laparoscopic BA has reduced mortality from 5.6% to 1.5% and morbidity from 40% to 15% [1,8,9].

Considering the obesity and expected hemodynamic disturbances, this method was also favored in this patient.

Our patient went through an intensive pre-habilitation regime, including medical management and chest physical therapy. All measures were taken to manage a complex airway and possible difficulty in intubation. A thoracic epidural was expected to provide effective postoperative pain management to minimize pulmonary complications in this obese patient. Invasive arterial and venous pressures monitoring was used to detect and manage dynamic fluctuations in hemodynamic parameters associated with intra-operative manipulation of the hypertrophic adrenal glands and the acute adrenal insufficiency that results from resection of bilateral adrenal glands.

As expected, a few episodes of blood pressure surges during the surgical manipulation of the hypertrophied gland required an epidural bolus and increment of volatile agent. However, this occurrence was not reported in the previous cases published with regards to BA for CD.

Acute withdrawal of cortisol following BA was managed perioperatively with IV hydrocortisone bolus given at induction and continuation of uninterrupted infusion throughout the surgery and the immediate postoperative period. The blood pressure drop observed in the immediate late intraoperative and immediate postoperative period was also reported frequently except in a case reported by Dhanukar et al. in 2007 [10,11,12].

Apart from hemodynamic instability, other complications include opportunistic infections, chest infections, thrombo-embolism, electrolyte and fluid imbalances in the peri-operative period [10,12,13]. This patient, DVT prophylaxis with enoxaparin was commenced 6 hours after completion of the surgery to reduce the perioperative thromboembolism.

After BA, patients need to be compliant with replacement glucocorticoid and mineralocorticoid therapy for life to prevent life-threatening acute adrenal crisis [1,14]. In a meta-analysis of studies with a 42-months follow-up, the adrenal crisis incidence ranged from 9%-64% (median 28%) [14].

Nelson's Syndrome is a long-term complication following BA for CD [15] An expanding pituitary mass, high circulating ACTH levels, and hyperpigmentation, mass effects include compression of the optic apparatus and visual field defects, headache, external ophthalmoplegias and hypopituitarism are features of this unfortunate complication [15]. The time interval between the bilateral Adrenalectomy and a diagnosis of NS of 0.5 years - 24 years [15]. Careful periodic evaluation is warranted after BA for the development of Nelson’s syndrome. In some centers, neoadjuvant pituitary radiotherapy is given to prevent development of Nelson’s syndrome [16,17]. However, as our patient was planning for a pregnancy, we did not consider cranial radiotherapy to preserve the HPO axis and will be monitoring the patient with clinical examination, ACTH levels and MRI scans when needed to recognize Nelson’s syndrome early. Successful pregnancies have been reported, despite all the metabolic derangements that result from BA [18-20].

CONCLUSION

The decision process leading to surgery for Bilateral Adrenalectomy for persistent Cushing's disease following several unsuccessful transsphenoidal surgeries, especially in a patient who desired to preserve hypothalamo-pituitary-ovarian function for future pregnancies is thought-provoking, which mandates a meticulous pre-operative pre-habilitation and management of intraoperative measures to prevent complications.

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