Case Report

Anaesthetic concerns during adrenalectomy for Cushing's syndrome with known hyperhomocysteinemia

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ABSTRACT

Maintenance of homeostasis during anaesthesia in the patient with two major metabolic disorders whose systemic effects either compliment or contradict each other is a challenge to the anaesthesiologist. A 25-year-old male patient with Cushing's syndrome and known hyperhomocysteinemia was scheduled for open adrenalectomy. Both these disorders compound the hypercoagulable state and differ in glucose metabolism. In addition, obesity, difficult airway, electrolyte and metabolic derangements that accompany Cushing's syndrome warrant special attention. He was on anticoagulant therapy and inferior vena cava filter following an episode of pulmonary thromboembolism with deep vein thrombosis. Perioperative hydrocortisone was administered. Thoracic epidural catheter was placed at T10–T11 interspace, standard general anaesthesia was administered without nitrous oxide. Patient was extubated following an uneventful procedure and discharged home on 10th post-operative day. Understanding the anaesthetic implications and the pathophysiological interactions of multiple metabolic disorders with a potential for multisystem involvement is key to the successful management of these patients.

Key words: Anticoagulants, Cushing's syndrome, hyperhomocysteinemia, pulmonary embolism

INTRODUCTION

Hyperhomocysteinemia and its association with vaso-occlusive disease and thrombosis are well-established[1] and may be an independent risk factor for cardiovascular disease and venous thrombosis. Hyperhomocysteinemia is due to the disrupted metabolism of homocysteine a sulphur containing aminoacid; leading to the accumulation of homocysteine with its varied symptomatology.

In Cushing's syndrome endogenous glucocorticoid excess is associated with a prothrombotic state that put patients at increased risk of vascular thrombosis that is responsible for the increased mortality of these patients.[2-5] Moreover, patients with hypercortisolism may have elevated levels of homocysteine.[6]

The hypercoaguable state produced by homocysteinemia and Cushing's syndrome and subsequent anticoagulation therapy, titration of the glycaemic levels and theoretical risk of using nitrous oxide create a unique anaesthetic challenge that must be carefully addressed. Medline search showed paucity of literature in the management of perioperative hypercoagulable state in the presence of these dual risk factors. Hence, we present a case of homocysteinemia with Cushing's syndrome and describe the anaesthetic implications in the perioperative period.

CASE REPORT

Permissions were obtained from the patient and Institutional Ethics Committee to report this case. A 25-year-old male with features of Cushing's

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syndrome was admitted to the hospital for right adrenalectomy. He had a history of superior sagittal sinus and left transverse sinus thrombosis 2 years back for which he was evaluated and found to have hyperhomocystenemia. He received anticoagulation therapy (tablet acenocoumarol 4 mg/day) and folic acid, vitamin B6 and B12 for 7 months, and the anticoagulation therapy was discontinued. Two years later he presented with pulmonary thromboembolism and deep vein thrombosis of left lower limb. He was immediately thrombolysed with injection streptokinase and inferior vena caval filter was placed and anticoagulation therapy was instituted with low molecular weight heparin (LMWH) and later with oral anticoagulants (tablet acenocoumarol 4 mg OD). Echocardiogram showed right atrial and ventricular dilatation, ejection fraction of 60%, trivial tricuspid regurgitation, moderate pulmonary regurgitation and pulmonary arterial hypertension with normal biventricular function. Therapy with tryptophan 25 mg, sildenafil 25 mg and atorvastatin was also initiated. Patient was evaluated for Cushing's syndrome in view of physical appearance and presence of thrombotic tendency despite controlled homocysteine levels. The diagnosis was confirmed by the high levels of serum cortisol. A computed tomography of the abdomen showed right adrenal mass. The patient was scheduled for open adrenalectomy a month later.

General examination revealed puffy moon face with facial plethora, red purple striae over thighs with body mass index of 26 kg/m^2 and American Society of Anaesthesiologists physical status of grade I. His airway examination revealed short thick neck, and Mallampati grade III suggesting difficult airway. The data of the pre-operative laboratory investigations is shown in Table 1.

Oral anticoagulant was stopped 5 days prior to surgery and was started on injection heparin 5000 IU 6th hourly. His premedication consisted of tablet pantoprazole 40 mg, and alprazolam 0.5 mg and rest of the medications were continued. Morning dose of heparin was not administered.

On the day of surgery injection hydrocortisone 100 mg was given intravenously (IV). Thoracic epidural was placed at T10–T11 interspace. Left radial artery and right internal jugular vein were cannulated for monitoring. The patient was pre-medicated with injection glycopyrrolate 0.2 mg and fentanyl 120 μg IV. Anaesthesia was induced with thiopentone 300 mg and after confirming mask ventilation injection atracurium was administered, and the airway was secured with 8 mm oral endotracheal tube. On laryngoscopy the Cormack Lehane grading was IIIb and intubation was performed using McCoy laryngoscope and gum elastic bougie. Anaesthesia was maintained with oxygen, air, isoflurane and titrated doses of atracurium; nitrous oxide was avoided. Epidural analgesia was activated with 0.25% bupivacaine and fentanyl in a ratio of 1:1 (1 ml containing 0.25 mg bupivacaine and 1 μg fentanyl) infusion and continued intra-operatively. Elastocrepe bandages were applied to prevent peripheral stagnation of blood before induction of anaesthesia. The intra-operative course was uneventful with minimal blood loss and lasted for 4 h. IV fluids administered were normal saline and Ringer's lactate, one litre each. Arterial blood gas was monitored hourly along with glucose levels. Recovery was unremarkable, and trachea was extubated after reversing the residual neuromuscular blockade and after meeting the criteria for extubation. The patient later was shifted to intensive care unit for continued monitoring. Post-operatively, analgesia (epidural), fluid, glucose electrolyte and acid-base imbalance were managed meticulously. Hydrocortisone 100 mg IV was administered on day 0 and day 1 and after that 50 mg 8th hourly for 2 days. Later tablet prednisolone 15 mg/day was given in divided doses. LMWH was started 6 h after surgery and epidural catheter was removed on 3rd post-operative day (POD) 2 h before the scheduled dose of heparin and heparin was

Table 1: Laboratory investigations

Parameter	Result	Reference range
Random sugar (mg/dl)	103	Up to 140
Blood urea (mg/dl)	18	15-40
Serum creatinine (mg/dl)	0.9 mg	0.9-1.4
Haemoglobin (g/dl)	14	13-17
PT (s)	11.5	10-13 [INR 1]
APTT (s)	31	22-32 [INR 1.2]
Total count (mm^3)	8700	4000-10,000
Serum cortisol (μg/dl)	47.5	8-25
DHEA (μg/dl)	222.7	280-640
ACTH (pg)	16.9	10-46
Urinary metanephrines (μg/day)	64.42	<350
Normetanephrines (μg/day)	514.5	0-600
Homocysteine (μmol/L)	7.5	7-10
Protein C (%)	120	70-160
Protein S (%)	60	60-150
Lupus AC (GPL/MPL)	1.22	1.20
ANA	Negative	

PT – Prothrombin time; APTT – Activated partial thromboplastin time; DHEA – Dehydroepiandrosterone; ACTH – Adrenocorticotrophic hormone; Lupus AC (GPL/MPL) – Anticardiolipin G phospholipid and M phospholipids; ANA – Antinuclear antibodies; INR – International normalized ratio

stopped on 6th POD. Oral anticoagulant was restarted after 24 h of surgery. Patient was mobilised from 3rd POD and was discharged on 10th POD with an advice to continue his routine medication.

DISCUSSION

The patient's hyperhomocysteinemic state was compounded with Cushing's syndrome with its complex derangement in haemostatic parameters. Together they confer an increased risk of coronary heart disease and cerebrovascular accidents, which are important determinants of the increased mortality.[3-6]

The normal role of homocysteine in the body is to control growth and support bone and tissue formation. The normal range in plasma is 7–10 μmol/L. In the urine, the level of homocysteine is in the same range. Plasma levels of 15–30 μmol/L are considered indicative of mild to moderate[7,8] hyperhomocysteinemia and in severe hyperhomocysteinemia, levels exceed 100 μmol/L and are because of genetic mutation. The disrupted metabolism of homocysteinemia leads to accumulation of homocysteine with its multisystemic manifestations. High levels of plasma homocysteine are usually associated with vascular injury by mechanisms of oxidative damage, vascular smooth muscle proliferation, promotion of platelet activation and aggregation. It also disrupts the normal procoagulant anticoagulant balance favouring thrombosis, stimulate growth of arteriosclerotic plaque, which leads to heart disease.[5,9] Homocysteine plasma levels above 10 μmol/L are associated with a doubling of vascular risk.[7] The resulting plasma levels over 12 μmol/L require aggressive folic acid supplementation.[8] Initiation of therapy with B12, folic acid, and B6 tends to normalize homocysteine levels in 4–8 weeks. Although vitamin supplementation is successful in decreasing total plasma homocysteine levels, anticoagulation therapy is required to prevent vascular occlusive pathology. In the present case, the patient had anticoagulation therapy for 7 months and later was put on supplemental therapy.

The incidence of thromboembolic events will be multiplied with the combination of the disorders.[3,5,7] This patient initially had a history of superior sagittal sinus thrombosis and found to have hyperhomocysteinemia of 59.7 μmol/L and 2 years later despite normal range of homocysteine levels had pulmonary thromboembolism and deep venous thrombosis. At this time, cortisol levels were very high with features of Cushing's syndrome. These patients require meticulous measures to prevent post-operative thromboembolism. This patient was treated with anticoagulants and had an inferior vena cava filter placed. Bridging therapy with heparin was started 5 days before the planned surgery. Intra-operative measures like monitoring central venous pressure for maintenance of euvolemia, elastocrepe bandage application were instituted. Post-operatively, LMWH and oral anticoagulants were started 6 and 24 h after surgery respectively[10] and the patient was mobilized early to prevent thromboembolism.

Both these metabolic disorders derange glucose metabolism, but have opposing effects.[11,12] In hyperhomocysteinaemia, the patients will suffer from hypoglycaemia, the mechanism being increased methionine leading to increased insulin release resulting in hypoglycaemia.[13] Insulin resistance is also described with homocysteinemia. However in Cushing's syndrome, the patients will be effected by hyperglycaemia. Hence, the combined effect on glycaemic control can be variable and unpredictable. In the present case, blood glucose and electrolytes were carefully monitored perioperatively, and the glucose levels were well within the normal range despite Cushing's syndrome and steroid therapy.

Patients with Cushing's syndrome are also the candidates for potential airway difficulties because of obesity. Our patient was intubated using gum elastic bougie and McCoy laryngoscope.

Literature shows that the use of N_2O-based anaesthesia increases plasma homocysteine and significantly impairs endothelial function and is a risk factor for post-operative cardiovascular morbidity in patients undergoing non-cardiac surgery.[14,15] The patients with mutations are at even more risk for fatal outcome.[16,17] Duration of anaesthesia is also important because prolonged exposure to N_2O causes a significant elevation of homocysteine levels than short term exposure.[18-20] Acute myelopathy, neurological deterioration and death have been reported after use of N_2O.[21] N_2O was eliminated in the management of this patient. Our patient was without any post-operative neurological complications.

This case report discusses several important anaesthetic issues relevant to the management of patients with

hyperhomocysteinemia and Cushing's syndrome including meticulous titration of anticoagulation therapy, glycaemic control, airway management and the potential risk of using nitrous oxide.

CONCLUSION

Understanding the anaesthetic implications and the pathophysiological interactions of multiple metabolic disorders with a potential for multisystem involvement is a key to the successful management of these patients as seen in the present case with hyperhomocysteinemia and Cushing's syndrome.

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