Laparoscopic adrenalectomy for phaeochromocytoma: a case series
Cheri Hotu, Richard Harman, Rick Cutfield, Nicola Hodges, Eletha Taylor, Simon Young

ABSTRACT

AIM: To describe our 13-year experience in laparoscopic adrenalectomy for phaeochromocytoma.

METHOD: We performed a retrospective analysis of case notes of 29 patients who underwent laparoscopic adrenalectomy for phaeochromocytoma between 2000 and 2013.

RESULTS: Twenty-nine patients (16 female), aged 16 to 67 years, underwent laparoscopic adrenalectomy for phaeochromocytoma. All patients were treated preoperatively with alpha-blocking agents. 80% were prescribed additional preoperative antihypertensive agents. 90% received antihypertensive agents intraoperatively. All patients received intraoperative magnesium sulphate for haemodynamic stabilisation. The mean operative time was 160 minutes. Nearly all of the patients experienced haemodynamic stability during surgery. Two patients required conversion to open adrenalectomy, due to severe intraoperative hypertension during tumour handling, and due to extensive intra-abdominal adhesions. Postoperative complications were minimal, and included blood loss, superior epigastric artery damage, and cellulitis at the laparoscopic port site. There was no perioperative mortality. The median length of stay postoperatively was 4 days. 24% were prescribed antihypertensive medication on discharge.

CONCLUSION: In our experience, favourable perioperative outcomes were achieved, demonstrating that laparoscopic adrenalectomy for phaeochromocytoma is a safe and effective procedure in the setting of experienced and skilled surgical, anaesthetic and medical teams delivering the perioperative care.

The laparoscopic approach to adrenalectomy, first described in 1992 by Gagner et al, has become the preferred option over open laparotomy for the removal of most adrenal tumours, functioning or non-functioning, and is considered a safe and effective surgical method. Although often associated with longer operative times when compared to open laparotomy, the advantages of laparoscopic adrenalectomy are in its association with less intraoperative and postoperative morbidity and complications. These include lower rates of intraoperative trauma and blood loss, a decreased need for postoperative analgesia, quicker recovery times and shorter hospitalisation periods. These benefits can lead to increased cost-effectiveness in most but not all cases. Vascular injury and bleeding can still occur with laparoscopic adrenalectomy, and when compared to the removal of aldosterone-secreting tumours, laparoscopic adrenalectomy for phaeochromocytoma removal has been associated with larger tumours, longer operative times and increased complication rates.

Intravenous (IV) magnesium sulphate has been shown to be an effective adjunct in the anaesthetic management of open adrenalectomy for phaeochromocytoma removal through its ability to decrease catecholamine release and control the cardiovascular instability associated with this procedure. One case report has described the effectiveness of magnesium sulphate during laparoscopic adrenalectomy for phaeochromocytoma in a paediatric patient. Publications on the use of magnesium sulphate in this setting are few. We found no published retrospective, clinical case series on laparoscopic adrenalectomy for phaeochromocytoma using adjunctive IV magnesium sulphate intraoperatively.
Method
We carried out a 13-year retrospective analysis of experience in laparoscopic adrenalectomy for phaeochromocytoma at a tertiary hospital in New Zealand between 2000 and 2013. The study was approved by the local district health board research review committee. As a clinical audit, it was given exemption from review by the regional ethics committee. Patient demographics, co-morbidities, family history, clinical presentation, biochemical and radiological investigations, preoperative blood pressure (BP), and medications were reviewed. The use of intraoperative antihypertensive agents, vasopressor agents and magnesium sulphate was recorded. Intra- and postoperative outcomes, including mean operative times, intraoperative BP, blood loss, postoperative complications, IV analgesic requirements and postoperative duration of hospital stay were reviewed, as were BP and antihypertensive medication at discharge. The surgery was performed by a laparoscopic surgeon, experienced in performing laparoscopic adrenalectomy for the removal of adrenal tumours, including phaeochromocytoma. Anaesthetic support was provided by an experienced anaesthetic team. Perioperative care was also provided by experienced nursing staff. Pre- and postoperative antihypertensive therapy was overseen by an endocrinologist.

Results
Twenty-nine patients (16 female and 13 male) underwent laparoscopic adrenalectomy for phaeochromocytoma. Ages ranged from 16 to 67 years; the mean age was 46 years. There were 22 European, three Māori, two Samoan, one Niuean and one Thai patient. Most cases involved sporadic tumours. One patient had a history of Von Hippel-Lindau (VHL) syndrome with associated renal, ocular and intra-cerebral stigmata. His father and brother also had VHL syndrome. Another patient had a simultaneous renal cell carcinoma and a positive family history for phaeochromocytoma, but tested negative for the VHL gene mutation. One patient had multiple endocrine neoplasia (MEN) 2B with a history of medullary thyroid cancer. Another patient had a history of bilateral phaeochromocytomas and had previously undergone a left adrenalectomy for phaeochromocytoma removal. Three patients had one or more first-degree relatives with a history of phaeochromocytoma.

The majority of patients underwent investigation for phaeochromocytoma based on clinical suspicion from their presenting symptoms and signs. Nineteen patients presented with either sustained or paroxysmal hypertension, and hypertensive crises during surgical procedures were reported in five patients. Episodic headaches and palpitations were reported in 14 patients respectively. Seven patients experienced profuse sweating, and five patients had episodic chest pain. Four patients experienced anxiety attacks and one patient presented with a manic episode. Four patients had incidental findings of an adrenal mass, detected in one patient during a renal tract ultrasound scan for investigation of chronic kidney disease, and during computed tomography (CT) scanning in the other three patients. One patient had undergone a staging CT scan for bowel cancer, the second patient had an abdominal CT scan for investigation of abdominal pain, and the third patient underwent a pulmonary CT scan following an episode of haemoptysis.

All of the patients underwent measurement of 24-hour urinary catecholamines or metanephrines, or plasma metanephrines, and in some cases both tests were done. Elevated catecholamine or metanephrine levels were seen in all of the patients.

The patient with previous resection of a contralateral phaeochromocytoma, and the patient with VHL syndrome, were both found to have elevated urinary catecholamines during routine surveillance screening. Diagnostic imaging modalities used included CT imaging in 16 patients and magnetic resonance imaging (MRI) in 16 patients. Six patients had a metaiodobenzylguanidine (MIBG) scan in addition to MRI or CT.

Eighteen patients had right-sided adrenal phaeochromocytomas, the remainder had left-sided lesions.

All of the patients received alpha-blocking agents preoperatively. Phenoxybenzamine
was used in 26 patients, doxazosin in two patients, and labetalol in one patient. Twenty-three patients (80%) were taking other antihypertensive medications preoperatively in addition to the above medications. Beta blockers were prescribed in 15 patients, calcium channel blockers in 10 patients, thiazide diuretics in two patients, and an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) in one patient, respectively. At hospital admission, the mean (SD) preoperative systolic and diastolic BPs were 142 (24) mmHg and 86 (12) mmHg respectively. Median (IQR) preoperative systolic and diastolic BPs were 144 (124-155) mmHg and 85 (80–90) mmHg respectively.

The mean operation time was 160 minutes (59–260 minutes). The patient with renal cell carcinoma underwent a right laparoscopic adrenalectomy and right nephrectomy. Another patient underwent a simultaneous right hemicolectomy for colon cancer. All of the patients received intraoperative magnesium sulphate, administered as boluses of 2.5 to 4 grams (g) and in infusions of 1 to 2.5 g/hour. Twenty-six patients (90%) received IV antihypertensive medication intraoperatively. Twenty patients received esmolol, five patients received glyceryl trinitrate, and 10 patients were administered sodium nitroprusside. Ten patients received more than one antihypertensive agent intraoperatively. Four patients experienced systolic BP spikes of ≥200 mmHg intraoperatively but this was for a brief duration (<2 minutes) in most cases. Two patients required conversion to open adrenalectomy, one patient developed severe intraoperative hypertension (270/160 mmHg) during tumour handling, and the other patient had significant scarring present between the tumour and the aorta. Thirteen patients received intraoperative vasopressor infusions. Noradrenaline was the most common vasopressor agent used. Five patients experienced brief episodes of intraoperative hypotension (systolic BP<80mmHg), but this was quickly corrected with the use of volume expanders and vasopressor administration. None of the patients developed intraoperative arrhythmias. Blood loss was <500 ml in 14 of the 16 patients who had this quantified. The maximum recorded blood loss was 1,200 ml. One patient sustained intraoperative damage to the left superior epigastric artery which required repair. Prolonged neuromuscular blockade was not reported in any of the cases.

Three patients required IV analgesia for >24 hours postoperatively. The patient who underwent open adrenalectomy after developing severe intraoperative hypertension received bupivacaine and fentanyl via an epidural infusion for 4 days postoperatively. Postoperative complications included cellulitis at a laparoscopic port site, urinary retention, and pneumonia in three respective patients. The median length of stay was 2 days preoperatively and 4 days postoperatively. Twenty-six patients had 6 days or less hospital stay postoperatively. The other three patients had 7, 13 and 14 post-operative days stay respectively. There was no perioperative mortality. On histological inspection, the mean tumour size was 45 mm (25–75 mm). Twenty-seven of the tumours were benign, one was multifocal and one was malignant.

Discussion
Phaeochromocytomas are rare, catecholamine-secreting tumours that arise from the chromaffin cells of the adrenal medulla. The annual incidence is approximately 0.8 per 100,000 person years. Untreated phaeochromocytomas are associated with a high incidence of morbidity and mortality. The most common symptom of phaeochromocytoma is sustained or paroxysmal hypertension. Other common symptoms include episodic headache, sweating and palpitations. Panic attack-type symptoms, generalised weakness, tremor and pallor are less common symptoms. Phaeochromocytoma has been associated with cardiomyopathy due to excess catecho-
lamine release, similar to stress-induced takatsuho cardiomyopathy.

Whilst most phaeochromocytomas are sporadic, approximately 30% are familial. VHL syndrome, MEN2, and neurofibromatosis type 1 (NF1) are the familial disorders associated with phaeochromocytoma. Following biochemical confirmation of the diagnosis, clinical practice guidelines recommend CT scanning of the adrenal glands as the initial imaging test, however MRI should be considered when there is evidence of metastatic disease or when limitation of radiation exposure is crucial, for example during pregnancy. MIBG scintigraphy is useful for locating metastatic paragangliomas, however positron emission tomography (PET)/CT scanning is the preferred imaging modality in patients with metastatic paragangliomas.22

The definitive treatment for phaeochromocytoma is surgical removal of the tumour.

Laparoscopic adrenalectomy has been shown to be a safe and effective procedure for the removal of adrenal tumours including phaeochromocytoma.316 For favourable outcomes to be achieved in the surgical management of patients with phaeochromocytoma, it is important that adequate perioperative care be delivered. While it is unclear whether all patients awaiting surgery for phaeochromocytoma removal need preoperative hypotensive treatment, there is evidence to suggest benefit in patients with BP >180/115 mmHg, and in those with complications of hypertension, including heart failure, coronary artery disease, stroke and dysrrhythmias, and during pregnancy.23

Haemodynamic changes, including an increase in heart rate and BP, are part of the normal physiologic response to stress and these predictably occur during laryngoscopy and tracheal intubation for any surgical procedure. Haemodynamic instability, in particular intraoperative hypertension, is common during phaeochromocytoma surgery due to an exaggerated release of catecholamines occurring throughout the different stages of airway management and surgery.22,24 with one series reporting intraoperative hypertension (systolic BP >200mmHg) in 58% of cases.25 Intraoperative hypertension can be severe and sustained, often requiring the use of potent antihypertensive agents to control it.24 Pneumoperitoneum induced during laparoscopic adrenalectomy, and in particular, handling of the phaeochromocytoma tumour can result in marked catecholamine release resulting in severe hypertension.24 Effective intraoperative management of BP is therefore crucial during phaeochromocytoma surgery. Careful handling of the tumour tissue, limited intra-abdominal pressure, adequate anaesthesia and the use of vasoactive agents are important components of achieving intraoperative BP stability and reducing the risk of complications secondary to elevated intraoperative BP. Rapid-acting antihypertensive agents that allow for a reduction of BP, without exerting a prolonged effect, can be particularly beneficial at the time of tumour removal. Intraoperative hypotension may also occur during surgery for phaeochromocytoma, particularly following tumour removal, with one series reporting intraoperative hypotension in 53% of cases.25 Proficient anaesthetic management with the use of volume expanders and vasopressor administration can prevent sustained episodes of hypotension from occurring.

There is limited information in the literature on the efficacy of adjunctive therapeutic agents to achieve haemodynamic stability intraoperatively in phaeochromocytoma removal. Magnesium sulphate, which acts as a calcium channel antagonist, has been shown to enhance cardiac and haemodynamic stability by inducing peripheral vasodilation and increasing anti-arrhythmic effects by inhibiting catecholamine release from the adrenal medulla, and by decreasing alpha-adrenergic receptor sensitivity to catecholamines.18,19,27 The resultant peripheral vasodilation leads to a decrease in systemic vascular resistance and a lowering of arterial systolic BP. The effectiveness of magnesium sulphate has been described in the control of severe hypertension in the setting of phaeochromocytoma crisis.28 Studies and case reports have shown high dose magnesium sulphate to be effective in reducing catecholamine levels during anaesthetic induction and
intubation, leading to a decrease in BP and heart rate.\textsuperscript{18,19,27} Serum magnesium levels between 2–4 mmol/l are associated with a significant attenuation of catecholamine output during tracheal intubation.\textsuperscript{18,19,27} Although catecholamine release resulting from tumour handling is not inhibited by the use of magnesium sulphate, the effectiveness of this agent during tumour handling is thought to be due to its ability to reduce alpha-adrenergic receptor sensitivity to catecholamines.\textsuperscript{18} Potential complications associated with magnesium sulphate include prolonged neuromuscular blockade,\textsuperscript{30} emphasising the importance of monitoring neuromuscular function in the immediate postoperative period, and the cautious dosing of muscle relaxants.

Our case series demonstrated favourable perioperative outcomes in patients undergoing laparoscopic adrenalectomy for phaeochromocytoma. Apart from one patient who developed severe, sustained intraoperative hypertension requiring conversion to open adrenalectomy, haemodynamic stability was maintained in the majority of patients, and while 10 of the patients required more than one antihypertensive agent during surgery, BP was controlled without difficulty in most cases, and sustained elevations of BP were not seen. Intraoperative hypotension also occurred infrequently and was non-sustained. Postoperative complications were minimal and there was no mortality. More than two-thirds of patients treated with antihypertensive therapy preoperatively (in addition to adrenergic receptor blockade) did not require these medications on discharge from hospital. Experienced surgical, anaesthetic and medical teams delivering a high standard of surgical and perioperative care to the patients likely contributed to favourable outcomes achieved.

Several limitations were identified in the study. The clinical data reviewed came from a single centre only, and the study's retrospective design precluded our ability to identify any causal relationship between intervention and perioperative outcomes. Another important limitation was around the accuracy and precision of manual recordings in the anaesthetic records of eight patients, resulting in difficulty to calculate parameters such as the mean and median intraoperative BP. The precise duration from incision to wound closure was difficult to ascertain in some of the cases due to limited recording of the specific stages of the operation within the patient notes. The mean operation time is likely to have been overestimated due to this factor. Also, the lack of a control group makes it difficult to conclude how much benefit magnesium sulphate had in addition to adequate preoperative alpha blockade and intraoperative antihypertensive use. A blinded placebo controlled study is therefore needed to further evaluate the utility of magnesium sulphate during laparoscopic adrenalectomy for phaeochromocytoma.
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Author information:
Cheri Hotu, Consultant Endocrinologist and General Physician, Post-Doctoral Fellow in Indigenous Health, Baker IDI Heart & Diabetes Institute Central Australia and Department of Medicine, Alice Springs Hospital, Alice Springs, NT, Australia; Richard Harman, Consultant Surgeon, Department of Surgery, Waitemata District Health Board, North Shore City; Richard Cutfield, Consultant Endocrinologist and General Physician, Department of Medicine, Waitemata District Health Board, North Shore City; Nicola Hodges, Senior Registrar, Department of Surgery, Counties Manukau District Health Board, Manukau City; Eletha Taylor, Consultant Surgeon, Department of Surgery, Auckland District Health Board; Auckland City; Simon Young, Consultant Endocrinologist and General Physician, Department of Medicine, Waitemata District Health Board, North Shore City.

Corresponding author:
Dr Simon Young, Department of Medicine, Waitemata District Health Board, Private Bag 93503, Takapuna, North Shore City 0740, New Zealand.
Simon.Young@waitematadhb.govt.nz

URL:

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