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Bilateral adrenalectomy for Cushing's disease

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Abstract
Purpose Review the indications, outcomes, and consequences of bilateral adrenalectomy (BLA) in patients with Cushing's disease.
Methods A literature review was performed.
Results The primary therapy for Cushing's disease is surgery, with medical therapy and radiation therapy relegated to an adjuvant role. BLA is indicated in cases of persistent disease following pituitary surgery or in situations where rapid normalization of hypercortisolism is required. When performed via the laparoscopic approach, BLA is associated with a significantly reduced morbidity compared to the traditional, open approach. Following BLA, patients are at risk for adrenal crisis and the concern of Nelson's syndrome. However, BLA leads to a rapid resolution of the signs and symptoms of CS and leads to an improved long-term quality of life.
Conclusion BLA should be considered in the treatment algorithm for patients with persistent CD after failed pituitary surgery, especially in patients who have severe consequences of hypercortisolism or desire pregnancy.

Keywords Bilateral adrenalectomy · Cushing's syndrome · Cushing's disease · Nelson's syndrome · Adrenal crisis

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Introduction

Cushing's syndrome (CS) is divided into two types: adrenocorticotrophin (ACTH) dependent (due to pathologic hypercortisolism due to excessive hypersecretion of ACTH) and ACTH-independent (CS due to a primary adrenal disorder). Up to 85 % of ACTH-dependent cases are due to an ACTH secreting corticotroph pituitary adenoma, called Cushing's disease [1]. The other cases are due to ectopic secretion of ACTH or corticotropin releasing hormone (CRH), and the most common cause is a bronchial carcinoid. The primary therapy of ACTH-dependent CS is surgery directed at the underlying source of the ACTH. In Cushing's disease 20–30 % of subjects require further therapy following surgery because of persistent disease [2]. Radiation therapy (RT) may be used to target the residual pituitary adenoma [3], although the delay in biochemical control and the risk of hypopituitarism relegate RT to a more adjuvant role. In cases of ectopic ACTH secretion, the underlying tumor is often undetected. In such cases of ACTH-dependent hypercortisolism, adjuvant therapy is necessary to normalize cortisol excess. For all causes of ACTH-dependent CS not cured by primary surgery, adjuvant medical therapy may be used. The Food and Drug Administration recently approved the somatostatin receptor ligand, Pasireotide and the glucocorticoid receptor antagonist, Mifepristone for use in Cushing's disease [4]. Other medical therapies that block the adrenal gland, including ketoconazole, metyrapone, and mitotane, or target the corticotroph tumor, including cabergoline, are used off-label to normalize cortisol secretion [2, 5]. In a recent study, Castinetti et al. [6] showed that ketoconazole may be effective in normalizing urinary free cortisol excretion in approximately half of subjects. Such medications may be useful in

management of CD, although there may be limitations due to variable efficacy or side effects.

ACTH-independent forms of CS are usually treated surgically with unilateral or bilateral adrenalectomy (BLA), depending on whether there is asymmetric (e.g., adrenal adenoma, carcinoma) or bilateral disease (including hyperplastic and macronodular disorders). The focus of this review will regard the use of BLA for treatment of ACTH-dependent Cushing's disease.

Surgical approach

In the past decade, the minimally invasive laparoscopic procedure has gained more universal acceptance than the open procedure. Laparoscopic adrenalectomy can be performed via a lateral transabdominal (LT) versus a posterior peritoneal (PR) approach. The LT procedure tends to be performed in subjects with a higher body mass index, larger adrenal tumor size, and other concomitant intraabdominal pathology [7]. The LT approach is performed in up to 70 % of medical centers [8] and is more commonly performed for ACTH-dependent CS [9]. In a recent review of 12 studies, Takata et al. [10] noted that the overall rates for mortality and complications following BLA were 2.4 and 13 %, respectively, and infectious and thromboembolic events comprised 41 and 18 % of the complications, respectively. Therefore, the mortality rate is very low, but the complications including infections and thrombotic events, likely exacerbated by hypercortisolism, are common in the postoperative period. These concerns need to be taken into account in the decision to proceed with BLA.

Ritzel et al. [11] analyzed the outcome of 23 studies (739 patients) who underwent BLA, including 426 open and 313 laparoscopic approaches. Open adrenalectomy was performed in 38 % of the patients via the transperitoneal approach and in 60 % via the retroperitoneal approach. Surgical outcome was similar between the procedures, as surgery-related 30-day mortality ranged from 0 to 15 % (median, 3 %) and 0–8 % (3 %) for open and laparoscopic procedures, respectively [11]. Interestingly, surgical mortality was lower for patients with Cushing's disease compared to ectopic CS, although the reasons underlying this finding are unclear. The laparoscopic approach resulted in lower morbidity (internal and incisional complications), blood loss, anesthesia exposure, and inpatient hospital days compared to the open approach [12, 13]. Hence, a laparoscopic approach is used for the majority of patients with CS, with conversion to an open procedure necessary in a small subset of cases. Of note, it is important that the adrenal glands are resected completely, and that the integrity of the adrenal capsules is carefully maintained [14]. Retained adrenal cortical cells can lead to subsequent ACTH driven hyperplasia and recurrence of CS. In a recent study, adrenal remnants were noted in 8 % of 36 cases, necessitating adrenal revision in one case [15].

The role of bilateral adrenalectomy

BLA is most often used in subjects where other modalities have failed and those who need rapid normalization of cortisol secretion due to profound consequences of hypercortisolism. The advantage of BLA is immediate control of hypercortisolism, in contrast to the delayed and inconsistent control in subjects who undergo RT or medical therapy. In addition, BLA is considered in subjects with persistent disease and are considering fertility, as the currently Food and Drug Administration approved medical therapies are not approved for use in pregnancy.

In cases with persistent ACTH-dependent CS despite surgery, BLA is often not considered until the subject has failed medical therapy and/or RT. Therefore, BLA is usually relegated to distant role in such patients. As shown in recent studies, BLA is performed after disease duration of 1.8–6.8 years [9, 15]. This finding demonstrates the frequent reluctance to proceed with BLA earlier in the therapeutic paradigm. However, recent studies suggest that BLA should be considered earlier in the treatment paradigm in lieu of other adjuvant therapies. For example, BLA may improve long term mortality compared to use of medical therapy alone. In a recent retrospective study by Morris et al. [16] of 65 patients (16 pituitary, 49 ectopic), 32 % were treated by medical therapy followed by BLA and 68 % by medical therapy alone. In this study, 55 % of patients in the medical therapy only group died, and steroid excess contributed to 71 % of complications. Of the BLA subjects, 29 % died, including all three patients with recurrent CS after BLA. These authors concluded that subjects treated only with adjuvant medical therapy were more likely to die from Cushing's-related sequelae compared to those who underwent BLA, and that BLA may be considered earlier in subjects with persistent CD [16]. These data add further support for considering BLA in the management paradigm in subjects with persistent CS.

Postoperative management

Following surgery, subjects will have primary adrenal insufficiency and will require lifelong glucocorticoid and mineralocorticoid replacement. Glucocorticoids should be initiated immediately following surgery (50–100 mg hydrocortisone every 8 h intravenously) with taper to oral and replacement doses of glucocorticoids as tolerated. In addition, mineralocorticoid replacement with fludrocortisone should be initiated following surgery as well. The dose of fludrocortisone can be monitored by monitoring blood pressure, and serum potassium and plasma renin levels.

Subjects with CS are at risk for thromboembolic events, and a recent meta-analysis of 15 studies with 567 patients reported 17 thromboembolic events (3 %) after adrenalectomy during the period of follow-up [11]. This translated into 4.8 thromboembolic events per 1,000 patient-years [11]. Therefore, the postoperative care should include use of mechanical tools such as pneumatic compression and ambulation as tolerated. Following surgery, serial imaging studies with magnetic resonance imaging (MRI) should be performed to assess for possible growth of the corticotroph adenoma, which could lead to Nelson's syndrome (see below).

Clinical outcomes

Following BLA, the majority of subjects note improvement in the clinical signs and symptoms of CS. In a recent meta-analysis, there was improvement in muscular weakness in 93 %, clinical stigmata in 77 %, hypertension in 80 %, diabetes mellitus in 75 %, menstrual cycle irregularities in 75 %, and fatigue in 70 % [11]. Eighty percent of subjects with obesity had weight loss. Of note, the hydrocortisone maintenance dose correlated with the persistence of morbidities after BLA [15]. This finding emphasizes the need for vigilance in preventing use of excessive glucocorticoid dosing for long term replacement.

CS is associated with significant emotional, medical and physical consequences, and recovery is often slow and delayed. The duration for recovery is a function of a number of factors, including glucocorticoid dosing, addition of physical exercise, psychological counseling, and effective replacement therapy for hypopituitarism if present. Hence, CS and its therapy may have a deleterious impact on quality of life for a significant time period. Because of postoperative morbidity following BLA, the quality of life may be further reduced, at least in the short run. In addition, the increased risk of adrenal crises (see below) because of the acquired primary adrenal insufficiency may further impede quality of life. However, BLA may lead to improvement in quality of life as well. Smith et al. [12] found that 86 % ($n = 28$) of CS patients felt overall improvement of their health status 1 year following BLA, although fatigue persisted in half. In a retrospective study with a mean follow up of 11 years (range 0.8–51 years) after BLA [15], quality of life remained impaired in 45 % of female patients and 17 % of the male patients with CS compared with a healthy population. Of note, the improvement in quality of life was similar to that of subjects with remission following transsphenoidal surgery [17]. These data indicate that BLA over the long run leads to a significant improvement in signs and symptoms, as well as comorbidities of CS, and leads to an overall sense of well-being similar to that of successful transsphenoidal surgery.

Long term complications

Adrenal crisis

One major postoperative concern is that of the risk of adrenal crisis, which can prompt emergency department visits for intravenous glucocorticoid administration. Adrenal crises in this situation can be precipitated by infection, trauma, or stress, and may be a significant source for impaired quality of life in such patients. The occurrence of adrenal crisis ranges from a median of 4.1 to 9.3 adrenal crises per 100 patient-years and may lead to premature death [11, 15]. Therefore, it is critical that subjects are educated on self-management of an adrenal crisis, as inadequate education may contribute to the extent of the adrenal crisis [18]. Our practice is to educate patients on self-administration of intramuscular glucocorticoids, as use may pre-empt an emergency room visit. Also, it is critical that subjects obtain a medical alert system to facilitate communication with the healthcare team in a crisis situation.

Nelson's syndrome

ACTH levels and pituitary directed MRI scans are monitored following BLA in order to assess potential growth of the primary corticotroph adenoma. It is important for clinicians to note that plasma ACTH levels often increase following BLA. In a recent study [15], ACTH levels increased from a median of 54 to 203 pg/ml after the BLA. Therefore, levels in this range are not necessarily concerning and should not lead to urgent intervention. However, Nelson's syndrome refers to a situation of expansion of the primary corticotroph adenoma following BLA, and is accompanied by an even more rapid and absolute rise in ACTH levels as well as hyperpigmentation. Nelson's syndrome occurs in 8–35 % of subjects who have undergone BLA and did not receive cranial radiation, and is usually noted within 3 years [19–22]. Risk factors for Nelsons' syndrome include young age and a high post-BLA plasma ACTH value, although clear ACTH cutoffs have not been defined [19]. The diagnostic criteria for Nelson's syndrome are not well delineated. One group of authors suggested the criteria should include evidence of an expanding pituitary mass and an elevated morning plasma ACTH >500 ng/l, in addition to progressive elevations of ACTH (a rise of >30 %) on at least three consecutive occasions [20]. Although corticotroph adenomas can enlarge during pregnancy in a woman who underwent BLA, pregnancy does not seem to accelerate the tumor growth compared with the natural course before pregnancy [23].

Management of Nelson's syndrome involves therapy directed at the expansile pituitary adenoma, including further surgery and use of radiotherapy [24]. Medical

therapy has in general been relatively ineffective for Nelson's syndrome. Cabergoline [25] and cyproheptadine [26] have been useful in a small number of subjects. There have also been case reports of use of the somatostatin analog, octreotide, in subjects with Nelson's syndrome [27]. A potential role use of the novel somatostatin analog, pasireotide, has been suggested for such patients [28]. Use of temozolomide has been suggested as well [29]. A protective role of radiation in preventing Nelson's syndrome has been suggested given the lower incidence of Nelson's syndrome is lower in subjects who received RT in some studies [3, 30], but not all studies. Whether RT should be administered routinely in a patient who underwent a BLA to prevent Nelson's syndrome is unclear.

Recurrence of CS

In a recent meta-analysis, <2 % experienced a relapse of CS with clinical signs of hypercortisolism following BLA [11]. This rare event presumably reflects growth of persistent adrenal rest cells either from incomplete surgery or through rest cells from embryologic derivation. In such patients, imaging should be performed to determine presents of residual/recurrent adrenal rest lesions which may be amenable to surgical excision. In such situations, adjuvant medical therapy as described above may be necessary to control hypercortisolism. Therefore, long term follow up is important to assess for potential recurrence of hypercortisolism.

Conclusion

BLA is a useful tool for the management of ACTH-dependent CS and, through the laparoscopic approach, results in improved surgical morbidity compared to the open approach. Though there are significant consequences to this procedure, including enhanced risk for adrenal crises and the concern of Nelson's syndrome, BLA leads to a rapid resolution of the signs and symptoms of CS and leads to an improved long-term quality of life. Therefore, BLA should be considered in the armamentarium for patients with persistent CD after failed pituitary surgery.

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