Original Article

Outcomes of Bilateral Adrenalectomy in Cushing's Syndrome

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Abstract

Context: The literature on outcomes of bilateral adrenalectomy (BADx) in Cushing's syndrome (CS) is scant. **Aims:** The aim of this study is to analyze the short- and long-term outcomes of patients who underwent BADx and to compare the outcomes among different etiologies of CS. **Settings and Design:** This is a retrospective analysis of patients who underwent BADx for CS at our center between 2005 and 2018. **Materials and Methods:** In all, 33 patients were studied for clinical outcomes, survival rates, and long-term complications. **Statistical Analysis:** All analyses were performed with SPSS software (version 21.0). **Results:** The mean age at surgery was 39.33 ± 15.67 years. The primary etiology for CS was Cushing's disease (CD) in 42.42%, ectopic source in 36.36%, primary pigmented nodular adrenocortical disease (PPNAD) in 12.12%, and adrenocorticotrophin hormone–independent macronodular adrenal hyperplasia (AIMAH) in 9.09% of patients. The median follow-up time was 72.77 months. Improvement in hypertension and diabetes status after surgery was seen in 78% and 76.19% of patients, respectively. Proximal myopathy improved in 68% of patients. Nelson's syndrome and adrenal crisis were seen in 21.4% of patients each on long-term follow-up. Total mortality after BADx was 33.3%. Mortality in the first 30 days after surgery was seen in five patients (15.15%). Higher cortisol levels at presentation and age more than 40 years were predictors of mortality. Among the Cushing's subtypes, PPNAD had the best prognosis followed by CD. Perioperative Infections were a major cause of mortality. **Conclusion:** BADx is an effective treatment for CS especially in patients with PPNAD and CD but carries a significant mortality rate too.

Keywords: Bilateral adrenalectomy, Cushing's syndrome, long-term outcomes, Nelson's syndrome, survival

Introduction

At first described by Harvey Cushing in 1932, Cushing's syndrome (CS) is a condition of prolonged glucocorticoid excess. Although CS is a rare disease with an incidence of only 0.7–2.4 million cases per year, untreated disease can cause significant morbidity and mortality. Therefore, prompt diagnosis and successful therapy are of paramount importance.[1-3] Bilateral adrenalectomy (BADx) is an important modality of treatment in Cushing's disease (CD) after failed pituitary surgery and unlocalized ectopic Cushing's syndrome (ECS). It is also indicated in adrenocorticotrophin hormone (ACTH)–independent macronodular hyperplasia (AIMAH) and primary pigmented nodular adrenocortical disease (PPNAD).[4]

There is paucity of data in Indian literature on long-term outcomes after BADx. The aim of our study was to study the long-term clinical outcomes, morbidity, and survival rates in CS after BADx.

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Materials and Methods

This study is a retrospective analysis of patients who underwent BADx at a tertiary referral university teaching hospital for CS between 2005 and 2018. A total of 40 patients underwent BADx. Of these 40 patients, 33 patients were operated for CS. Demographic, clinical, and laboratory data were collected from hospital electronic records and analyzed. Follow-up data were collected from follow-up visits, hospital records, and telephonic conversations. Indications for BADx were persistent glucocorticoid excess in CD following failed transsphenoidal surgery (TSS) once or more and/or radiotherapy, ECS where the source could not be localized, AIMAH, and PPNAD. The patients were categorized into the above categories based on clinical,

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biochemical, and radiological characteristics. The screening tests to establish hypercortisolemia were overnight dexamethasone supression test and a serum midnight cortisol. Following this, patients were subjected to a low-dose dexamethasone supression test for confirmation of diagnosis. Patients with plasma ACTH more than 10 pg/mL were categorized as ACTH-dependent CS. A high-dose dexamethasone supression test was performed in ACTH-dependent CS. Among the patients with ACTH-dependent CS, patients with pituitary adenoma >6 mm were categorized as CD. Patients with absence of pituitary lesions on dynamic magnetic imaging resonance (MRI), cortisol suppression of less than 50% on high-dose dexamethasone suppression test, and ACTH >90 pg/mL were categorised as ECS. Inferior petrosal sinus sampling (IPSS) was performed in three patients when HDDST was suppressed by more than 50%, but a pituitary adenoma was not localized on dynamic MRI. IPSS assigned ACTH to a peripheral source in all the three patients. IPSS could not be performed in three patients due to financial constraints and they opted for an upfront BADx. Patients were subjected to computed tomography (CT) abdomen and CT thorax (4/12 patients), 18 F-fludeoxyglucose (FDG) positron emission tomography (PET) CT (4/12 patients), and Gallium DOTANOC PET CT (4/12 patients) for localization of the ectopic source of ACTH. Standard steroid replacement following BADx was as follows: 100 mg intravenous (IV) bolus 1 h before procedure followed by 150 mg IV hydrocortisone in three divided doses or 8 mg/h infusion in the first 24 h of surgery. This was gradually tapered based on hemodynamic status and electrolyte values. Patients were discharged on an average of 30 mg oral hydrocortisone per day in three divided doses with or without fludrocortisone. On long-term follow-up, some of them were switched to prednisolone. Medical alert letter for stress dosing was given to all patients at the time of discharge. Patients were also taught intramuscular hydrocortisone injection technique to tide over any emergency. All patients were given perioperative low-molecular-weight heparin and deep vein thrombosis (DVT) stockings until ambulated. Pneumocystis carinii prophylaxis was also given.

Statistical analysis

Statistical analysis was done using SPSS software (version 21.0; IBM, Chicago, IL, USA). Continuous variables are reported as mean ± standard deviation or median values and ranges, whereas categorical variables are reported as absolute numbers and percentages. Overall survival was estimated using Kaplan–Meier plot. Independent sample *t*-test and Mann–Whitney *U*-test were used to compare the average parameters between two groups. Kruskal–Wallis test was used to compare the average parameters between three or more groups.

Results

A total of 40 patients underwent BADx between 2005 and 2018. Of these 40 patients, 33 patients were operated for CS and the remaining were operated for pheochromocytoma. The mean age at BADx was 39.33 ± 15.67 years. The median follow-up time was 72.77 months (1–134 months). The majority of the patients (26/33) had ACTH-dependent CS. The etiology of CS is summarized in Figure 1. The baseline characteristics of the patients are summarized in Table 1.

A total of 12 patients were categorized as ECS. The primary tumor was localized only in 4 of 12 patients which were gastrinoma with widespread liver and lung metastasis, meningioma, lung carcinoma, and a pancreatic carcinoid in one patient each. Patients with pancreatic carcinoid and gastrinoma continued to have symptoms of hypercortisolemia after surgical resection of the primary tumor. Patient with meningioma refused a brain surgery and lung cancer was inoperable. The tumor-producing ECS remained unlocalized in 8 of 12 patients on follow-up. Among the patients with CD, eight patients had undergone TSS once, three patients had undergone TSS twice, and two patients had undergone radiation therapy before BADx.

Surgical outcome

All 33 patients underwent BADx by the laparoscopic technique. Nine patients were treated with adrenolytic drugs preoperatively. Oral ketoconazole was used in seven patients, while two patients were treated with IV etomidate infusion. Of the 33 patients, 5 patients (15.15%) died within the first 30 days after adrenalectomy.

Deep venous thrombosis was seen postoperatively within the first 6 months in two patients, of which one patient had pulmonary embolism.

Clinical outcome

Among the 33 patients who underwent BADx, 6 patients did not have hypokalemia preoperatively. All 27 patients with hypokalemia had normalization of potassium levels after surgery.

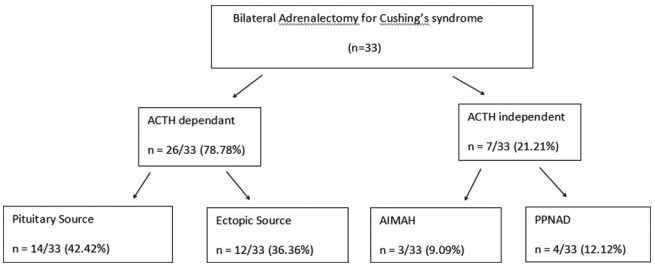

Figure 1: Etiology of Cushing's syndrome in patients who underwent bilateral adrenalectomy

Table 1: Baseline patient characteristics

Total patients	33
Male/female	13/20
Age at the time of surgery (mean±SD)	39.33±15.67 years
Serum Cortisol prior to surgery (mean±SD)	39.88±22.32 µg/dL
Comorbidities	
Diabetes mellitus	25/33 patients
Systemic hypertension	25/33 patients
Osteoporosis	11/33 patients
Coronary artery disease	3/33 patients
Chronic obstructive pulmonary disease	2/33 patients

SD: standard deviation

Long-term clinical outcomes were assessed in 28 patients who did not have surgery-related mortality. Significant improvement in hypertension was seen after surgery. Of the 22 patients who were hypertensive before surgery, antihypertensives were stopped immediately post op in 13 patients (59%) and 1 year after surgery in 2 patients (9%). Dose of antihypertensive medications were reduced 1 year after surgery in 2 of 22 patients (9%). Continuation of antihypertensive medications at the same dose was required in 5 of 22 patients (22.7%).

Of the 28 patients, 21 patients were diabetic before surgery. There was improvement in diabetes status after surgery in 16 of 21 patients (76.19%). Medications could be stopped in 5 of 21 patients (23.8%) after a mean duration of 1.1 years. Of the 21 patients requiring insulin preoperatively, 7 patients could be managed with oral antidiabetic drugs postoperatively. The dose of insulin was reduced in 4 of 21 patients (19%). The same dose of insulin was continued in 5 of 21 patients (23.8%).

Data on proximal myopathy were available in 25 of 28 patients. The majority of the patients [17/25 (68%)] reported significant improvement in proximal muscle power after surgery. There was no improvement in proximal myopathy in 2 of 25 patients (8%), and 6 of 25 (24%) patients did not have symptoms of proximal myopathy prior to surgery. Among the female patients, 10 patients had menstrual irregularities before surgery. Regularization of the menstrual cycles after surgery was seen in 4 of 10 patients (40%). Psychiatric disturbances improved in 50% of the patients.

Mortality

Total mortality after BADx was 33.3% (11/33 patients) [Table 2]. Mortality in the first 30 days after surgery was seen in five patients (15.15%). The diagnosis in these patients was ECS in three patients and AIMAH in two patients. Septicemia was the major cause of mortality (60%). One patient succumbed to pulmonary embolism and another patient succumbed to intestinal perforation with sudden massive intraperitoneal bleed. None of the patients with CD had surgery-related mortality.

In addition to surgery-related deaths in five patients, mortality was due to myocardial infarction ($n = 4$), recurrent pyelonephritis with sepsis ($n = 1$), and massive pulmonary embolism unrelated to surgery ($n = 1$).

The mean age at mortality was 45.36 years. In patients who had surgery-related mortality, the mean time between BADx and death was 13.4 days. In patients who had mortality unrelated to surgery, the mean time between BADx and death was 48.6 months.

The mean preoperative cortisol value in patients who expired was 51.55 ± 28.22 µg/dL compared with 34.05 ± 16.52 µg/dL in patients with long-term survival. The difference in cortisol values between the two groups was significant ($P = 0.047$).

The mean survival following BADx was 90.64 months. PPNAD had excellent survival rates with 100% probability of survival at 1, 2, and 5 years of follow-up. CD had good survival rates of 91.7%, 83.3%, 74.1%, and 59.3% at 1, 2, 5, and 10 years of follow-up, respectively. ECS and AIMAH had

Table 2: Etiology of Cushing's syndrome, associated comorbidities, and cause of death

Patient	Age at mortality/sex	Etiology	Postop survival	Cause of death	Comorbidities
1	51/M	CD	24 months	Myocardial infarction	Diabetes mellitus, systemic HTN, osteoporosis with multiple vertebral collapse
2	32/M	PPNAD	101 months	Massive pulmonary embolism	Esthesioneuroblastoma
3	48/F	CD	96 months	Pyelonephritis, sepsis	Osteoporosis with L1 vertebral collapse, paraparesis, recurrent UTI, diabetes mellitus, systemic HTN
4	65/F	ECS	3 months	Myocardial infarction	Diabetes mellitus, systemic HTN, osteoporosis
5	46/F	CD	56 months	Myocardial infarction	Diabetes mellitus, systemic HTN, CKD on maintenance hemodialysis
6	41/F	CD	12 months	Myocardial infarction	Diabetes mellitus, systemic HTN
7	64/M	ECS	17 days	Pneumonia, fungal septicemia, renal failure	Diabetes mellitus, systemic HTN, COPD
8	16/F	AIMAH	10 days	Pneumothorax, pulmonary embolism	Multiple dorsolumbar and lumbar compression fractures
9	46/M	AIMAH	6 days	Colonic perforation, sepsis, ARDS	Diabetes mellitus, systemic HTN, coronary artery disease
10	65/F	ECS	12 days	Pneumonia, sepsis, ARDS, renal failure	Diabetes mellitus, COPD, coronary artery disease
11	25/M	ECS	22 days	Intestinal perforation/sudden massive intraperitoneal bleed	Diabetes mellitus, systemic HTN, lumbar compression fracture

ARDS: acute respiratory distress syndrome; CD: Cushing's disease; COPD: chronic obstructive pulmonary disease; ECS: ectopic Cushing's syndrome; AIMAH: adrenocorticotrophin hormone–independent macronodular adrenal hyperplasia; PPNAD: primary pigmented adrenal nodular disease

poor survival rates with 1 year probability of survival at 68.6% and 33.3%, respectively. Kaplan–Meier curve for survival is depicted in Figure 2.

The mean survival in patients aged less than 40 years was 112.47 months compared with 68.28 months in patients age >40 years. The difference in survival between the two groups was significant with a *P* value of 0.05.

The mean duration of symptoms before BADx was 38.8 months in patients who expired compared with 25.4 months in patients with long-term survival. The difference was, however, not significant ($P = 0.163$).

Long-term complications

Nelson's syndrome (NS) and adrenal crisis were the primary long-term complications after BADx. Of 33 patients, 6 patients (21.4%) experienced at least one adrenal crisis defined by the need for IV glucocorticoid administration. NS occurred in 6 of 28 patients (21.4%) and was seen after a mean period of 32 months after BADx. The mean ACTH level in these patients was 966 pg/mL. Treatment for NS included radiation therapy in three patients and surgical pituitary adenectomy in one patient. The mean preop ACTH value in patients with CD who developed NS was 61.94 ± 73.46 pg/mL compared with 21.97 ± 7.31 pg/mL in patients who did not develop NS. The difference in ACTH values between the two groups was not significant ($P = 0.604$).

Discussion

Although BADx is a potentially curative treatment option for patients with CS, data on outcomes of BADx in these patients are scarce. Our data demonstrate that BADx is an effective treatment option for selected patients with CS but still carries significant mortality primarily related to the severity of the underlying hypercortisolism and associated comorbidities.

Surgical mortality is an important measure to assess the safety of the procedure. Surgical mortality of 15.15% seen in our series was comparable to published literature showing a surgical mortality rate of 0%–15%. As reported in other studies, septicemia was the major cause of surgical mortality in our study.[5] As the cortisol excess blunts the immune response in these patients, it is extremely important to take measures to prevent infections as it could prove fatal. Associated comorbidities such as chronic obstructive pulmonary disease and coronary artery disease were frequently seen in our patients with surgical mortality. Preoperative cortisol value was also a predictor of mortality. The mean survival in patients younger than 40 years at the time of surgery was significantly higher. The benefits and risks should be assessed carefully in patients with associated comorbidities before undertaking BADx.

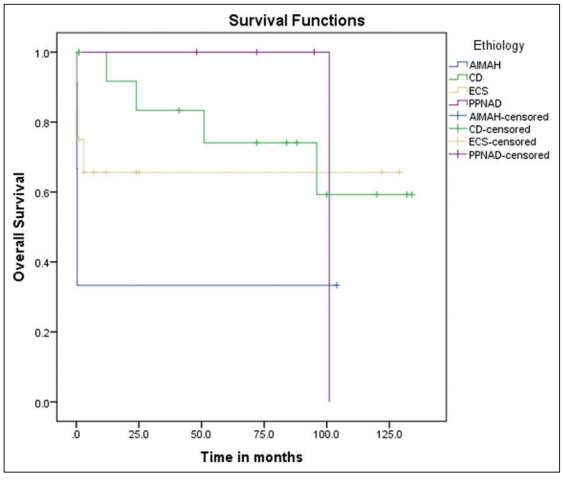

Figure 2: Survival in different subtypes of Cushing's syndrome

Long-term survival rate after BADx was significantly higher in CD in our series in comparison to ECS in accordance with published data.[5] We also found excellent survival rates in patients with PPNAD. Treatment for PPNAD involves BADx because of high recurrence risk after unilateral or partial adrenalectomy.[6]

In the series published by Carney and Young on PPNAD, BADx was performed in 48 patients (65% of the total number ofcases) and led to cure of CS. About 35% of patients experienced persistence or recurrence of CS after an initial improvement with subtotal or unilateral adrenalectomy and required completion of total adrenalectomy.[7]

Myocardial infarction was the major cause of nonsurgical death in our series. In a meta-analysis by Ritzel *et al.*, the main cause of death in CS over long-term follow-up was stroke, followed by myocardial infarction.[5]

BADx is an effective treatment resulting in remission of symptoms of hypercortisolism. None of the patients in our series had clinical recurrence of symptoms of hypercortisolism. Previous studies have reported similar data with regard to clinical recurrence of symptoms which makes BADx an effective treatment option in the treatment of CD.[8,9] Remission of hypercortisolism achieved by medical therapy is significantly lower, and severe side effects are seen with long-term use. Therefore, medical treatment is currently not considered to be an effective alternative to BADx. Medical treatment is, however, a good option in the preoperative period as an interim measure.[10] About 27.2% of our patients received medical treatment preoperatively in the form of oral ketoconazole or IV etomidate. Data from the ERCUSYN study showed that 20% of patients were treated with medical therapy before surgery. The most commonly used drugs were ketoconazole (62%), metyrapone (16%), and a combination of both (12%).[11]

Our data showed improvement in nearly all Cushing's-related comorbidities such as diabetes, hypertension, muscle weakness, and electrolyte abnormalities. Psychiatric morbidity and menstrual irregularities did not change distinctively which is in accordance with earlier studies.[5]

Adrenal crisis remains a dreaded sequela of BADx. In our series, 21.4% of patients developed at least one episode of

adrenal crisis requiring IV steroid replacement. Prevalence of adrenal crisis varied between 9% and 64% with a median rate of 28% in other series.[5] In a recent study of patients treated by BADx, 36.3% of patients develop at least one episode of adrenal crisis during a median follow-up of 80.5 months.[12] NS is another long-term complication seen after BADx. About 21.4% of patients in our study developed NS. Published data on NS show an incidence of 0%–47% with a median of 21% at a median follow-up of 61 months.[5]

Conclusion

In conclusion, BADx is an effective treatment option for patients with CS but carries a significant risk of mortality too. Preexisting comorbidities and infections are a major cause of surgical mortality. The benefits and risks have to be carefully considered in such patients, and all precautions to prevent infections and DVT have to be instituted. Long-term follow-up for complications such as adrenal crisis and NS is important.

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Conflicts of interest

There are no conflicts of interest.

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