

Long-term Outcomes of Unilateral Adrenalectomy in Patients with Dominant-side Adrenal Hyperplasia

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ABSTRACT

Introduction: Usual treatment for patients with aldosterone-producing adrenal adenoma is adrenalectomy, whereas adrenal hyperplasia is generally treated medically. Selective adrenal venous sampling (AVS) has been adopted to differentiate between adenoma and hyperplasia. A previous ratio used in our institution for the diagnosis of adenoma proved to be too low. As a result, a disproportionate number of patients with a preoperative diagnosis of adenoma were operated and subsequently found to have hyperplasia.

Materials and methods: This prospective study evaluated the long-term outcomes of unilateral laparoscopic adrenalectomy in the setting of lateralizing aldosterone hypersecretion caused by adrenal hyperplasia.

Results: Twelve patients with unilateral excess aldosterone production due to hyperplasia underwent dominant side adrenalectomy. Long-term follow-up (mean 12 years) of these patients showed that blood pressure decreased from a mean of $163.4 \pm 17.5/100$ to $131.5 \pm 9.7/80$ mmHg ($p < 0.05$), and the number of antihypertensive drugs decreased from 4.3 ± 0.7 to 2.2 ± 0.9 ($p < 0.05$). Mean potassium level increased from 3.7 to 4.2 mEq/L and the plasma aldosterone level decreased from 26.5 to 10.1 ng/dL.

Conclusion: Dominant side adrenalectomy in patients with primary aldosteronism (PA) due to hyperplasia results in long-term clinical improvement. This procedure should be considered in selected patients with lateralization confirmed by venous sampling.

Keywords: Adrenal hyperplasia, Adrenal venous sampling, Adrenalectomy, Primary aldosteronism.

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INTRODUCTION

Primary aldosteronism is the most common form of endocrine-induced hypertension, and is caused by autonomous aldosterone production from the cortex of one or both adrenal glands. Patients with PA typically present with hypertension, high plasma aldosterone levels associated with low plasma renin activity (PRA), and varying degrees of hypokalemia and metabolic alkalosis.¹ The prevalence of PA is as high as 20% in patients with resistant hypertension.^{2,3} The two main causes of PA are adrenal hyperplasia, which is usually bilateral and estimated to be present in about 95% of patients, and aldosterone-producing adenoma (APA), found in 5% of all cases.^{4,5} The treatment of choice for patients with APA is adrenalectomy, due to high success rates in resolving hypokalemia in all patients and cure or alleviation of hypertension in 60 to 80% of patients.⁶ In contrast, the acceptable treatment for adrenal hyperplasia has been only medical, due to bilateral adrenal involvement.

Selective AVS has been adopted to differentiate between adenoma and hyperplasia, but the correct ratio for selectivity and lateralization is not yet certain. Rossi et al⁷ suggested ratios for selectivity ≥ 1.1 and for lateralization ≥ 2 . Eventually, this ratio for the diagnosis of adenoma proved to be too low, but until 2005 the criteria suggested by Rossi et al⁷ were used in our medical center. Consequently, a considerable number of patients with adrenal hyperplasia underwent adrenalectomy. The aim of the present study was to evaluate the long-term outcomes of unilateral laparoscopic adrenalectomy of these patients with adrenal hyperplasia who had undergone dominant side adrenalectomy.

MATERIALS AND METHODS

In the 5-year period from 2001 through 2006, patients with refractory hypertension, increased plasma aldosterone concentration (PAC), and PRA greater than 50 ng/mL/hour were evaluated. The diagnosis of PA was confirmed either by a standard normal saline test [2 L intravenous (IV) in 4 hours], which was considered positive when PAC failed to decrease below 5 ng/dL at hour 4, and/or when 24-hour urinary aldosterone excretion after oral salt loading (12 gm per day for 4 days) was above 12 μ g/day in the presence of urinary sodium excretion greater than 200 mmol/day.

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All patients underwent high-definition computed tomography (CT) scan with IV contrast. Nineteen patients underwent AVS by an experienced invasive radiologist. Another five patients refused AVS and continued to be treated medically for hyperaldosteronism.

To ensure consistency due to the circadian rhythm of aldosterone, catheterization of the right femoral vein was accomplished in all patients between 10:00 AM and 12:00 AM. Patients were kept supine for 2 hours prior to AVS. Spironolactone was discontinued at least 4 weeks before the laboratory tests and AVS.

For measurements of blood aldosterone (A) and cortisol (C), two blood samples were obtained from each adrenal vein and from the infrarenal inferior vena cava (IVC). Normal morning plasma cortisol values were 5 to 25 µg/dL.

The criteria for selectivity index in this group of patients was $C_{\text{adrenal}}/C_{\text{IVC}} \geq 1.1$ and lateralization was considered positive when $A/C_{\text{dominant}}/A/C_{\text{nondominant}} \geq 2$, as established by Rossi et al.⁷ When lateralization of aldosterone secretion was established, laparoscopic unilateral adrenalectomy was proposed to all patients and performed after informed consent was obtained. After surgery, adrenal specimens were reviewed by two independent pathologists who used standard histological classification criteria.

Since the operation, all patients were followed prospectively through regular outpatient clinic visits (mean follow-up time is 12 years). Blood pressure and all laboratory findings were recorded. Medical treatment was changed as needed by the physician in charge of the hospital's Hypertension Treatment Unit.

The study was approved by the Institutional Helsinki Committee.

Statistical Analysis

Statistical evaluation included the paired t-test to compare differences between preoperative and postoperative blood pressures, serum potassium, and number of anti-hypertensive drugs. Statistical analysis was performed using Statistical Package for the Social Sciences 12.0 for windows. A p-value <0.05 was considered significant. Results are expressed as mean ± standard deviation.

RESULTS

An AVS was attempted in 19 patients and 18 procedures were technically successful (in one patient, catheterization of the right adrenal vein was unfeasible). Among these, five patients declined AVS and continued to be treated medically, as no adrenal mass was detected on CT scan. There were no complications following the procedure. The mean dominant to nondominant aldosterone/cortisol

ratio was 15.9 (2.1–50.8) on the left side and 7.9 on the right. The mean ratio of cortisol adrenal/cortisol IVC used to set up adrenal selectivity was 15.27 (1.2–60.4) on the left side and 1.9 (1.2–3.3) on the right.

Based on the AVS findings, 14 patients who met the criteria of unilateral aldosterone excess production were operated upon for a suspected adrenal adenoma. The mean age of the patients was 57 (34–81) years, with 8 males and 6 females.

Abdominal CT scans were performed in all 14 patients before surgery. In all these patients, an abnormal finding suspicious of an adenoma was found, mainly enlargement of one gland. In retrospect, in the two patients with an adenoma, a definite right adrenal mass was apparent. In 7 of the 12 patients with hyperplasia, a left adrenal mass was shown and another patient had a right adrenal mass (size range 6–24 mm). In the remaining four patients, diffuse enlargement of the left gland was seen in two and no adrenal pathology was seen in the other two. Of the four patients who did not have evidence of lateralization on AVS and who were not operated on, mild unilateral adrenal enlargement was seen in one patient and no abnormality in the adrenals was noted in three.

All operations were done laparoscopically, using a transperitoneal approach. During surgery, the entire gland was removed based on the preoperative AVS findings, regardless of the macroscopic appearance. There were no conversions to open surgery, no perioperative morbidity and no mortality. All patients were discharged 2 to 3 days after surgery and were followed up at the outpatient clinic of the hospital at 3-month intervals.

The final pathology report showed that 12 (86%) patients had adrenal hyperplasia: Nodular hyperplasia in six and diffuse hyperplasia in the remaining six patients. Only two patients (14%) had a benign adenoma. The pathological specimens were reviewed independently by two experienced pathologists.

When the final postoperative pathology was reported, all CT scans were reviewed retrospectively and the preoperative findings were shown to be accurate. Among the 12 patients with hyperplasia, lateralization by AVS occurred on the left side in 11 and on the right in 1, concurrent with the CT findings.

In the two patients with an adenoma, normalization of blood pressure was achieved after surgery. Among the 12 patients who were eventually diagnosed with adrenal hyperplasia, blood pressure control improved in all but one after surgery (Table 1). Mean systolic pressure decreased from 163.4 ± 17.5 to 131.5 ± 9.4 mmHg and diastolic pressure from 100 ± 4.2 to 80.0 ± 7.3 mmHg ($p < 0.05$ for both). The PAC decreased after surgery in

Table 1: Comparison of pre- and postoperative values (n = 14)

Variable	Preoperative value	Postoperative value	p-value
<i>Blood pressure (mm Hg)</i>			
Systolic	163.4	131.5	<0.05
Diastolic	100	80	<0.05
No. antihypertensive medications	4.3	2.2	<0.05
PAC (ng/dL)	26.5	10.1	<0.05
Serum potassium (mEq/L)	3.7	4.2	<0.05

all patients from 26.5 (9.9–49.0) to 10.1 ng/dL (4.1–16.7 ng/dL) ($p < 0.05$). Blood pressure continued to be poorly controlled in only one of the 12 patients despite a combination of four drugs including spironolactone at a dose of 200 mg/day.

The number of drugs needed to control blood pressure in this group of patients decreased from an average of 4.3 ± 0.7 before surgery to 2.2 ± 0.9 after surgery ($p < 0.05$). Before surgery, all patients were treated with maximum doses of antihypertensive drugs, reflecting a true decrease in the antihypertensive treatment following adrenalectomy. Only two patients with diffuse hyperplasia needed the reintroduction of spironolactone during follow-up. A significant decrease in aldosterone levels was demonstrated in all 12 patients. A significant long-lasting increase in blood potassium levels was also achieved.

DISCUSSION

Primary hyperaldosteronism is a frequent cause of refractory hypertension. The increasing prevalence of PA is largely due to the introduction of the PAC/PRA ratio as a screening test. The validity of the ratio in cases of very low or undetectable levels of PRA has been questioned and the requirement of a PAC > 15 ng/dL has been shown to increase the screening ratio sensitivity. Gallay et al⁸ used a threshold PAC/PRA ratio greater than 100 to screen a population of poorly controlled hypertensive patients. Fifteen of the 90 patients they tested met the required criteria and the diagnosis of PA was confirmed. While the accuracy of imaging in the detection of adrenal masses is improving, the presence of laboratory PA in a patient with hypertension remains a true challenge. Most secreting tumors are small (10–15 mm) and cannot be detected by the best imaging devices. Furthermore, the presence of an adrenal mass can be due to a nonfunctioning incidentaloma or macronodular hyperplasia. The results of the present study further emphasize misleading CT findings in patients with suspected PA. Visualization of unilateral aldosterone production with dexamethasone-suppressed adrenal scintigraphy using I nor-cholesterol is generally

of little help in these cases. Consequently, AVS has gained importance in detection of lateralization in PA patients, and it is considered effective in the diagnosis of unilateral oversecretion of aldosterone.

In the present study, we prospectively enrolled patients with refractory hypertension and laboratory findings consistent with PA, to undergo AVS, which was accomplished in all but one. This high percentage of success was similar to that reported by Rossi et al.⁷ Unilateral laparoscopic adrenalectomy was performed in 14 patients with adrenal lateralization and CT scan findings suggestive of adrenal adenoma, based on the criteria suggested by Rossi. The results of the pathologic specimens, reviewed independently by two experienced pathologists, showed a high proportion of hyperplasia (12; 86%), compared with benign adenomas in only 2 (14%) patients.

These results further emphasize the poor correlation between CT findings and the adrenal pathology. Two of six patients diagnosed with diffuse adrenal hyperplasia had unilateral masses, suggesting an adenoma. Furthermore, all patients with nodular hyperplasia had also unilateral masses on CT.

The results also showed that the lateralization ratio adopted by our institution based on Rossi's criteria was not diagnostic for adenomas. Indeed, different criteria for assessing the selectivity and lateralization of the adrenal glands at AVS have been reported. According to the new guidelines, the selectivity to confirm successful cannulation should be higher than 2.5 and higher than 4 with cosyntropin infusion.⁹ The recommended lateralization ratio for the diagnosis of adenoma is now higher than 2.5.^{1,10}

Until 2005, we used the criteria recommended by Rossi et al considering that it was based on a report that, for the first time, systematically assessed the different cutoff values for selectivity and lateralization. Weinberger et al¹¹ proposed the use of stimulation with adrenocorticotrophic hormone (ACTH) throughout AVS, to improve the detection of a lateralization in PA, particularly in those cases with cyclic secretion of aldosterone. Stimulation of adrenal activity with ACTH was not included in the protocol used by us at the time, because a later report by Rossi et al¹² did not find any benefit in the ACTH-related stimulation of aldosterone secretion, even when using simultaneously placed adrenal vein catheters.

The results of the present study show that a ratio ≥ 1.1 for selectivity and ≥ 2 for lateralization, as previously used, were too low for the diagnosis of an adenoma. As a result, a disproportionate number of patients with a preoperative diagnosis of adenoma were operated and subsequently found to have hyperplasia. The use of the

low lateralization ratio could also explain the results toward the left side as noted in 11/12 of the patients.

However, this bias gave us the opportunity to prospectively evaluate a relative large group of patients with dominant side hyperplasia that otherwise would have been treated only medically.

In this patient population, resection of the dominant side hyperplasia resulted in prolonged clinical improvement in terms of normalization of blood pressure, with a concomitant significant reduction in the number of drugs used, resolution of hypokalemia, and almost normalization of aldosterone levels. Previous studies reported similar results in unilateral hyperplasia (nodular and diffuse) as a source of excess aldosterone production.^{6,13,14} As in the current study, the presumed diagnosis prior to surgery was adrenal adenoma, but pathology findings were consistent with adrenal hyperplasia. In spite of the diagnosis of diffuse hyperplasia, resection of the dominant hyperplastic side resulted in clinical improvement.

CONCLUSION

In conclusion, the long-term clinical improvement obtained after unilateral adrenalectomy in our patients supports the concept that the presence of aldosterone lateralization at AVS may represent *per se* an indication for surgery in patients with refractory hypertension and hyperaldosteronism. We acknowledge that this inference needs a larger number of patients before being applied more broadly. Longer follow-up is also needed to confirm the long-term improvement in blood pressure in patients with unilateral adrenal hyperplasia, as well as to evaluate the possible recurrence of PA in the remaining gland.

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