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Outcomes of adrenalectomy in patients with unilateral primary aldosteronism: a review

Short running title: Adrenalectomy for unilateral primary aldosteronism

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Abstract

Aldosterone hypersecretion in primary aldosteronism is unilateral (aldosterone producing adenoma and primary unilateral hyperplasia) or bilateral (idiopathic adrenal hyperplasia). Laparoscopic adrenalectomy is nowadays the preferred approach to treat patients with unilateral primary aldosteronism. We review the outcomes of this intervention in recently published series. Laparoscopic adrenalectomy has a morbidity of 5 to 14%, mortality below 1% and a mean hospital stay around 3 days. It generally results in the normalization of aldosterone secretion and in a large decrease of blood pressure and antihypertensive medication, but normotension without treatment is only achieved in 42% of all cases. Normotension following adrenalectomy is more likely in young and lean women with recent low grade hypertension than in obese men with long-standing high grade hypertension or a family history of hypertension. However, individual prediction of the blood pressure outcome is not accurate and predictors of hypertension cure should not be used to select patients for surgery. Age, associated health conditions and preferences of the patient are more relevant to this end.

Keywords

Hyperaldosteronism; Adrenalectomy; Minimally Invasive Surgical Procedures; Treatment Outcome; Prognosis; Spironolactone.

Introduction

Aldosterone hypersecretion in primary aldosteronism (PA) can be bilateral (idiopathic adrenal hyperplasia or IAH) or unilateral (aldosterone producing adenoma or APA, primary unilateral hyperplasia or PUH). APA is a benign tumor varying in diameter from 7 to 35 mm, with no burden directly related to the space occupied and no risk of malignant transformation [1]. PUH can be diffuse or nodular, with poorly capsulated nodules ranging from microscopic to 6 mm [2]; in the latter case, the term “unilateral micronodular hyperplasia” may be used.

The goals of treatment in PA are to reduce the morbidity and mortality associated with sustained aldosterone hypersecretion and to improve the patients' quality of life. Health consequences of PA are partly mediated by high BP and low serum potassium. However, the cardiovascular and renal consequences of high BP are more severe in patients with PA than in patients with essential hypertension and similar levels of office BP. It is therefore assumed that sustained aldosterone hypersecretion induces target organ damage through genomic effects mediated by the mineralocorticoid receptor and possibly also by direct, non genomic effects [3].

Treatment objectives in patients with PA are therefore to reduce BP, correct hypokalemia, and to prevent or reverse the cardiovascular and renal alterations directly caused by aldosterone excess. The most logical way to achieve these objectives in patients with unilateral PA is to suppress aldosterone hypersecretion by removing the culprit adrenal. Although aldosterone antagonists have the theoretical disadvantage of preventing only the genomic effects of hyperaldosteronism, they are a suitable alternative in patients who refuse or are not candidate for surgery.

In the following sections we will firstly describe laparoscopic adrenalectomy and its morbidity; secondly we will consider potential alternative interventions to treat unilateral PA; thirdly we will summarize the outcomes and outcome predictors of laparoscopic adrenalectomy in these patients, with reference to medical treatment whenever possible.

Laparoscopic adrenalectomy

Since the first description of laparoscopic adrenalectomy in 1992 [4], the approach of adrenal surgery has been totally modified and laparoscopy has become the gold standard owing to its lower morbidity and shorter hospital stays. Subsequently, there was a significant increase of the proportion of patients with PA referred for minimally invasive adrenalectomy (27% after the introduction of laparoscopy vs. 13% before, $p < 0.05$) [5].

Practical details

To preclude the risk of hypokalemia-induced arrhythmia during anesthesia, hypokalemic patients should be provided potassium chloride or aldosterone antagonists before surgery [6]. Aldosterone antagonists may also suspend the chronic suppression of aldosterone secretion in the contralateral gland and thereby prevent postoperative hypoaldosteronism. Except comorbidities that could contraindicate laparoscopy per se, there is no technical reason that can avert from unilateral laparoscopic adrenalectomy for PA [7]. Obesity is not a contraindication but operating time correlates with the body mass index for both the transperitoneal or retroperitoneal laparoscopic approaches [8].

A large series illustrated the drawbacks and advantages of both approaches [9]. The lateral transperitoneal laparoscopic approach provides a wider exposure and therefore a more complete exploration of the abdomen, whereas the retroperitoneal approach avoids difficult exposure due to adhesions in patients with previous intra-abdominal surgery. This study shows that both approaches have similar outcomes when patients are well selected. The mean operating time of laparoscopic adrenalectomy, the rate of complications and the length of hospital stay vary depending on the indication and the approach used. The mean operative time of laparoscopic adrenalectomy in major institutional series is a between 2 to 3 hours, with a 3.4% conversion rate to open surgery and a mean hospital stay around 3 days [10].

Laparoscopic adrenalectomy usually requires three to four ports to introduce the instruments. Although technically challenging, laparoscopic single-port surgery using the transumbilical approach is less invasive [11]. Robot-assisted laparoscopy is feasible and safe but more expensive and without documented advantage over conventional laparoscopy [12,13].

Outpatient laparoscopic adrenalectomy is possible [14]. The feasibility conditions are: a disease other than pheochromocytoma, age younger than 65 years, tumor size smaller than 6 cm, no significant cardio-respiratory diseases, first case of the day to be managed in the surgical program, residence less than 30mn from the hospital by car, and no more than three antihypertensive agents. Over 22 outpatient procedures, the mean operating time was 57 min (range 15-120 min), the most frequent complications were pain and nausea.

Morbidity

The assessment of surgical morbidity is difficult because of the lack of standardized classification. The pooled mortality in major institutional series published up to 2005 (all indications confounded) was 0.4% (4/1083) [10]. There was no perioperative death in the largest series published afterwards (0/520) [15]. The incidence of non fatal complications ranges from 5 to 14% [6,10]. The most frequent severe complication of laparoscopic adrenalectomy is bleeding requiring transfusion or conversion to open surgery [10]. Compared with open adrenalectomy, the rate of wound, infectious, and pulmonary complications is much lower. In the large series already mentioned, major complications occurred in 1.3% of patients (7/520: pneumothorax, pneumonia, myocardial infarction, heart failure, blood loss requiring transfusion) and minor complications in 14.4% (mainly temporary relaxation and/or hypoesthesia of abdominal wall) [15]. Laparoscopic adrenalectomy appears to have a low morbidity but the teams that report their data are usually very experienced, with only one or two specialized surgeons operating all patients. Several cases of major complications outside referral centers have been reported [16].

Alternatives to laparoscopic adrenalectomy

Other surgical approaches

Partial adrenalectomy is an alternative to total adrenalectomy. It can be advocated since APA is always benign, and usually small, solitary, and located peripherally on the outer surface of the adrenal cortex. Moreover the adjacent cortex is always functioning, either normal or hyperplastic but never atrophied [17]. However, the rationale of partial adrenalectomy is still disputed since 10 to 25% of patients with unilateral PA have multiple adjacent nodules and there is no mean to be sure that the bigger lesion is the one responsible of the hypersecretion [2,18,19]. A review of 22 series (417 patients) found no unexpected complication of partial

adrenalectomy and similar surgical outcomes to total adrenalectomy [20]. A recent randomized controlled trial compared partial and total laparoscopic adrenalectomy in 212 patients with APA [21]. The operative time was the same for both approaches but blood losses were significantly higher with partial adrenalectomy, although no transfusion was needed. No major complication was observed with either approach. In the end, partial adrenalectomy is feasible and safe to remove an APA. However, the benefit of this adrenal sparing approach is questionable because the risk of a contralateral tumor that would subsequently require adrenalectomy is very low in patients with an APA. In addition

Non surgical approaches

Several alternatives to surgery have also been proposed for unilateral PA, such as percutaneous ethanol injection, arterial embolization and more recently percutaneous radiofrequency ablation. The risk of failure and the lack of pathological examination of the adrenal are the main drawback of these techniques. The main exclusion criteria for these procedures are a tumor over 4 cm, out of reach or ill-located (close to the aorta, to the kidney...). The treatment of APA with one to three ethanol injections in five patients cured PA with no other complication than periprocedural pain [22]. Selective adrenal arterial embolization in 33 patients with an APA resulted in a decrease of more than 20UH of the adrenal and the cure rate of PA was 82% [23]. Most patients experienced flank pain after the procedure, 30% had fever, 30% had labile blood pressure, and 15% had pleural effusion. A series of 24 patients that did undergo CT-guided percutaneous radiofrequency ablation for APA has been reported [24]. Adenomas remained hypolucent without contrast enhancement 3 to 6 months after the procedure in 100% of the patients and PA was cured in 96% (23/24 patients). However the complication rate was 17% with one small pneumothorax and 3 retroperitoneal hematomas

Outcomes of laparoscopic adrenalectomy

In this chapter we summarize the results observed in series published since 2000 with ≥ 50 consecutive patients from a single institution operated for unilateral PA (Table 1). Patients from these series were almost all operated after 1992. Older series are unlikely be representative of current practice because (i) the threshold of hypertension was lowered to 140/90 mmHg by the JNC5 in 1992 [25]; (ii) the aldosterone:renin ratio is widely used as a screening tool, independently of serum potassium levels, since 1990-1995 [26]; and (iii) laparoscopic adrenalectomy was first reported in 1992 and has become the preferred procedure since then [4]. Owing to these three changes, the clinical profile of PA patients who are sent to surgery is different since 1992 than it was before. It should be noted that patients from these series were assessed after medium term follow up (from a few months to a few years). Evidence is lacking regarding long term outcomes and especially the incidence of recurrent PA.

Potassium and hormonal outcomes

Surgery cures hypokalemia in $> 95\%$ PA and abolishes aldosterone hypersecretion in $> 90\%$ in patients with unilateral PA [33,35,36,39,43,45]. Persistent hyperaldosteronism is possible after surgery even if adrenal venous sampling (AVS) was performed to ascertain lateralization [33,45], as also reported in smaller series [46-48].

Blood-pressure outcome

Adrenalectomy produces a large decrease in systolic BP (typically -25 to -40 mmHg) and in the number of antihypertensive medications prescribed (typically -1 to -2 drug classes) [28-32,37-39,41,44]. However, BP changes are highly dependent on medication changes and only one study proposed to make a composite outcome out of these two variables [31]. This BP outcome score was neither derived from nor validated on actual patient data; its validity therefore remained to be evaluated. One single study attempted to predict the BP decrease after surgery [32]. However, it did not take medication changes into account and the predictors were weak. For instance, the mean systolic BP decrease was -25 mmHg after surgery and was only 3 mmHg less (-22 instead of -25 mmHg) in patients with a 0.5 mmol/l higher level of serum potassium before surgery, the most powerful predictor of unfavorable outcomes [32].

Patients should be warned that hypertension is not always cured. The pooled cure rate was 42% with significant heterogeneity across the series included in this review (Figure 1). Even when adrenalectomy does not cure hypertension, it usually leads to a clinically relevant improvement in the control of hypertension, with lower BP levels and/or less antihypertensive medication required. As a result, hypertension was cured or improved in 74 to 100% of cases in the series included in this review (Table 1). However, the definition of improvement differed in each series, precluding any pooled estimate of its occurrence.

Many predictors of hypertension cure or persistence have been reported (Table 2). Considering only factors that remained significant in at least one multivariate analysis, hypertension is less likely to be cured after adrenalectomy in patients with unilateral PA who are males, older, with a family history of hypertension, longer duration of hypertension, higher preoperative BP, more drug classes, higher BMI, higher serum potassium concentrations, lower estimated GFR, higher 24-h urinary aldosterone/active renin ratio, or evidence of arteriolosclerosis (Table 2). Of note, having unilateral PA ascertained by AVS was never found to be a predictor of good outcome after surgery [27,44], and has even been associated with worse outcomes [32,33]. Likewise, among patients with unilateral PA diagnosed by AVS, those with higher a lateralization index do not have a better outcome [41].

The relevance of these predictors of hypertension cure for selecting patients for surgery should not be overemphasized. First, the validity of multivariate analyses is threatened by small sample sizes and several studies found no association with hypertension cure for each of the supposed predictors (Table 2). Second, the multivariate models provide only a weak prediction of hypertension cure in individual patients. For example, according to the only prediction model validated to date, number of antihypertensive medication ≤ 2 , a body mass index ≤ 25 kg/m², a duration of hypertension ≤ 6 years and female sex are the best predictors of hypertension cure following adrenalectomy [34]. However, even if none of these features was present in an individual patient, he still had a 25% probability of being completely cured by an adrenalectomy in the validation cohort. Third, the focus on hypertension cure obscures the likely cure of hypokalemia and hyperaldosteronism and improvement of BP levels achieved even in patients with persistent hypertension after surgery.

No study has directly compared the BP outcome in patients with unilateral PA treated with spironolactone vs. adrenalectomy. However, the increase in serum potassium and decrease in BP reported in patients with unilateral PA treated with spironolactone are similar to those reported with adrenalectomy, even after a long follow-up duration [49].

Other outcomes

Many studies have shown that the structural heart changes seen in patients with primary aldosteronism – mostly left ventricular hypertrophy – resolve or greatly improve after adrenalectomy [50-54]. Although spironolactone may appear less potent than adrenalectomy in improving left ventricular hypertrophy [51,52,55], studies with longer follow-up have shown that the improvement is slower but similar at the end [54]. A prospective study with long follow up compared PA patients who were treated by adrenalectomy (unilateral disease) or spironolactone (unilateral or bilateral disease) to patients with essential hypertension [56]. The composite endpoint – myocardial infarction, stroke, any type of revascularization procedure, and sustained arrhythmias – did neither differ between these patients with PA who received a specific treatment and patients with essential hypertension, nor did it differ between PA patients treated with adrenalectomy or spironolactone.

Compared to otherwise similar patients with essential hypertension, patients with PA have a relative glomerular hyperfiltration that translates into increased GFR and low grade urinary albumin excretion. These changes are reversible after adrenalectomy in patients with unilateral PA [57-64]. Because of the reversal of relative hyperfiltration, adrenalectomy often unmasks hypertensive kidney disease with moderately decreased GFR. These results are also observed in PA patients treated with spironolactone [58-60,63,64].

Taken as a whole, patients with PA seem to have the same likelihood of glucose metabolism disorders than otherwise similar patients with essential hypertension [65,66]. Biochemical indexes of insulin resistance may improve after adrenalectomy [52,59], but this does not appear to translate into a clinically significant improvement of glucose metabolism [65].

One single study evaluated the impact of adrenalectomy on the quality of life in unilateral PA: patients experienced a significant improvement of their subjective well-being, which was lower than in the general population pre-operatively [67]. Unexpectedly, patients with PA treated with spironolactone experience a comparable benefit, although the improvement in quality of life appears to be slower [68].

Benefit – risk and cost – effectiveness assessment

As we have just seen, reduction of BP, correction of hypokalemia, and prevention or reversal of the cardiovascular and renal alterations can be achieved in patients with unilateral aldosterone hypersecretion by adrenalectomy or by the long-term prescription of aldosterone antagonists. Patients' preferences should be taken into account. Candidates for surgery should be told that the presence of an aldosterone-producing adenoma poses no threat of cancer and informed about the expected outcomes of surgery (benefits and risks, see above).

A primitive cost-effectiveness analysis performed for 50-year old PA patients found that adrenalectomy, with a 35% cure rate and a 85% improvement rate, was a cost saving option thanks to lifelong drugs withdrawal [69]. Younger patients have a longer life expectancy and therefore derive an even greater benefit from surgery. They also carry the smallest anesthetic risk. Early diagnosis of unilateral PA is therefore important. Patients with resistant hypertension may also derive a significant benefit, especially if compliance is an issue or if spironolactone is ineffective or not well tolerated. The benefit-risk ratio is more balanced in older patients, especially if their antihypertensive medication has compelling indications and

must be continued irrespective of BP levels, such as beta-blockers for coronary artery disease or angiotensin-converting enzyme and spironolactone for heart failure.

Conclusion

Laparoscopic adrenalectomy is an appealing therapeutic option for patients with unilateral PA. Some factors are statistically associated with hypertension cure after adrenalectomy but should not be used to select patients for surgery because they fail to identify a significant number of patients that will be cured. Moreover, they ignore the large BP and/or medication decrease and the direct benefit associated with the suppression of aldosterone hypersecretion in patients who remain hypertensive after adrenalectomy. Only the few patients who are at high surgical risk and those with a short life expectancy should be advised against surgery. On the other hand, patients should not be pressed to undergo surgery if they prefer not to, because a fair body of evidence suggests that lifelong treatment with mineralocorticoid antagonists is a valuable alternative to surgery. Other medical options, like aldosterone synthase inhibitors, may also be available in the near future. Best practice is to discuss treatment options with the patient even before performing AVS.

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Table 1. Series published since 2000 with blood pressure follow-up after adrenalectomy for unilateral PA in at least 50 consecutive patients

Figure 1. Hypertension cure rate after adrenalectomy for unilateral PA in series published since 2000 with at least 50 consecutive patients

Table 2. Predictors of hypertension cure following adrenalectomy in series published since 2000 and including at least 50 consecutive patients

Table 1. Series published since 2000 with blood pressure follow-up after adrenalectomy for unilateral PA in at least 50 consecutive patients

Institution	Years of inclusion	Patients followed	Patients cured	Definition of improvement	Patients cured or improved
Rochester, Mayo Clinic [23]	1993-1999	93	31 (33%)	BP decrease or fewer drugs	92 (99%)
Padova, University hospital [24]	1988-2002	98	71 (72%)	Less medication required for BP control	95 (97%)
Tokyo and Yokohama, Social Insurance Central General Hospital and Yokohama Rosai Hospital [25]	1995-2005	69	44 (64%)	None provided	Not available
Sendai, Tohoku University Hospital [26]	Not available	61	23 (38%)	BP decrease	61 (100%)
Sydney, University of Sydney Endocrine Surgical Unit [27]	1995-2005	53	18 (34%)	BP < 140/90 mmHg with equal or fewer drugs, or hypertensive but requiring fewer drugs	48 (91%)
Padova, University hospital [28]	Not available	50	15 (30%)	BP < 140/90 mmHg or fall of systolic and/or diastolic BP > 10%, on the same or reduced number of drugs and/or daily doses	50 (100%)
Paris, HEGP [29]	1993-2004	168	53 (32%)	Systolic BP < 140 mmHg and/or diastolic BP < 90 mmHg or diastolic BP decrease \geq 15 mmHg, for patients remaining on the same or less medication	124 (74%)
San Francisco, University of California San Francisco [30,31]	1994-2005	100	35 (35%)	BP decrease or fewer drugs	95 (92%)
Essen, Kliniken Essen-Mitte [32]	1994-2007	160	48 (30%) ^a	Systolic BP \leq 140 mmHg with reduced medication	139 (87%)
Ann Harbor, University of Michigan [33]	1996-2007	62	10 (16%)	BP < 140/90 mmHg with medication	53 (85%)
Paris, Broussais [34]	1997-1999	58	23 (40%)	BP < 140/90 mmHg with medication	43 (74%)
Taiwan, Chang Gung University College of Medicine [35]	1987-2006	52	32 (62%)	None provided	Not available
Ancona, Polytechnic University of	1994-2006	54	21 (39%) ^a	Systolic BP \leq 140 mmHg with reduced	47 (87%)

				medication	
Marche [36]					
Taiwan, University Hospital [37]	1999-2007	150	95 (63%) ^b	BP decrease with lower dosages of drugs	145 (97%)
Philadelphia, University of Pennsylvania [38]	2001-2007	57	12 (21%)	Systolic BP decrease > 10 mmHg with the same number of drugs, or SBP within 10 mmHg from preoperative value with fewer drugs	51 (89%)
Paris, Pitié Salpêtrière [39]	1997-2008	57	33 (58%)	Fewer drugs	56 (98%)
Wuhan, Tongji Hospitals [40]	2002-2007	93	54 (58%)	None provided	Not available
Marburg, University Hospital Giessen and Marburg [41]	1993-2009	54	20 (37%)	None provided	Not available

BP: blood pressure. Patients cured if BP < 140/90 mmHg without medication except ^a systolic BP < 140 mmHg without medication and ^b BP < 140/90 mmHg without medication in more than 75% of measurements

Table 2. Predictors of hypertension cure following adrenalectomy in series published since 2000 and including at least 50 consecutive patients

Risk factor	Associated in univariate analysis	Associated in multivariate analysis	Not associated
Being female	4 studies [32] [27] [39] [36]	1 study [31]	7 studies [37] [28] [24] [23] [38] [41] [40]
Younger age	5 studies [32] [39] [36] [23] [41]	5 studies [37] [31] [27] [24] [34]	4 studies [28] [35] [38] [40]
Absence of diabetes	1 study [37]	No study	No study
Absence of cardiovascular disease	1 study [37]	No study	No study
No history of essential hypertension in first-degree relatives	2 studies [37] [36]	2 studies [23] [40]	3 studies [31] [39] [24]
Shorter duration of hypertension before surgery	5 studies [32] [31] [39] [36] [23]	5 studies [37] [28] [24] [40] [41]	2 studies [35] [34]
Lower preoperative BP	3 studies [28] [39] [35]	2 studies [37] [40]	5 studies [27] [24] [23] [38] [41]
Lower number of prescribed antihypertensive classes	5 studies [27] [39] [36] [24] [38]	3 studies [31] [23] [41]	4 studies [37] [28] [35] [40]
Preoperative normalization of BP	1 study [30]	No study	No study
Preoperative normalization of BP on monotherapy with high-dose spironolactone	No study	No study	2 studies [30] [24]
Lower body mass index or weight	3 study [28] [39] [41]	2 studies [37] [31]	2 studies [24] [40]
Low serum potassium levels	1 study [31]	1 study [34]	9 studies [37] [27] [28] [39] [35] [24] [23] [41] [40]
Higher estimated GFR or lower creatinine concentration	2 studies [39] [34]	2 studies [37] [41]	4 studies [35] [24] [38] [40]
Presence of proteinuria	No study	No study	1 study [37]
Higher left ventricular mass index	1 study [34]	No study	1 study [28]
Presence of arteriosclerosis	No study	1 study [28]	No study

Higher urinary aldosterone excretion	1 study [23]	No study	1 study [34]
Higher 24-h urinary aldosterone/active renin ratio	No study	1 study [34]	No study
Higher plasma aldosterone concentration	No study	No study	10 studies [37] [31] [27] [39] [35] [24] [34] [38] [41] [40]
Lower plasma renin concentration or activity	2 studies [31] [39]	No study	5 studies [37] [35] [34] [38] [40]
Higher aldosterone:renin ratio	2 studies [34] [23]	No study	8 studies [37] [31] [28] [39] [35] [24] [38] [40]
Furosemide upright test	1 study [25]	No study	No study
Captopril test	1 study [25]	No study	No study
Typical adenoma on imaging or pathology	2 studies [32] [31]	No study	4 studies [37] [39] [23] [38]
Larger adenoma	3 studies [31] [39] [34]	No study	5 studies [27] [28] [24] [41] [40]
Smaller adenoma	1 study [25]	No study	5 studies [27] [28] [24] [41] [40]
Smaller adrenal gland	1 study [27]	No study	No study
Lateralization established by CT rather than AVS	1 study [30] [29]	No study	2 studies [23] [41]
Higher lateralization index	No study	No study	1 study [38]
Adenomectomy (vs. adrenalectomy)	1 study [32]	No study	No study

BP: blood pressure; GFR: glomerular filtration rate; CT: computed tomography; AVS: adrenal venous sampling

