Hypertension Outcomes of Adrenalectomy for Unilateral Primary Aldosteronism

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Abstract

Purpose: To evaluate laboratory and clinical results after unilateral adrenalectomy in patients with primary aldosteronism (PHA).

Methods: A cross-sectional analysis was performed using data from patients who underwent transperitoneal laparoscopic adrenalectomy for PHA, between January 2008 and December 2019. Surgical indications were based on adrenal venous sampling without ACTH stimulation. Analyses included patient demographics; preoperative clinical, pharmacological, laboratory, and radiological data; and postoperative results assessed after a median of 4 months. Antihypertensive drug use was quantified by estimating the daily defined dose (DDD) of antihypertensive medication, thus enabling standardised comparison of dosage between the drug classes. Statistical assessments included univariable and multivariable logistic regression analysis.

Results: This study enrolled 87 patients. The patients were taking 5.4 DDD of antihypertensive medication before surgery, and 3.0 DDD after surgery. In 45 cases (52%), the aldosterone-to-renin ratio normalized after surgery (“laboratory cured”), while 21 patients (24%) required no antihypertensive drugs after surgery (“clinically cured”). Among the 66 patients who were not clinically cured, 51 (77%) had a reduction of their DDD. Thus, surgery had a positive effect on hypertension control in 72 cases (83% of all enrolled patients). Multivariable logistic regression showed that clinical cure of hypertension was independently associated with female gender, absence of diabetes mellitus, and DDD < 4.

Conclusion: A majority of patients undergoing unilateral adrenalectomy for PHA achieved markedly improved hypertension control, despite almost halving their antihypertensive medication. About a quarter of patients were cured and able to cease using all antihypertensive drugs.

Introduction

Primary hyperaldosteronism (PHA) is a disease caused by aldosterone hypersecretion from the adrenal cortex, and is among the most common causes of secondary hypertension. Between 5–10% of patients with arterial hypertension exhibit PHA and in primary clinical care, PHA is found in up to 4.3% of hypertensive patients. Moreover, the PHA prevalence is as high as 13% in patients with severe hypertension, 17–23% in those with resistant hypertension, and 34% in patients with obstructive sleep apnea. [1, 2] PHA is associated with increased risks of cardiovascular, cerebrovascular, and renal morbidities. [3, 4] In approximately 95% of cases, PHA is caused by an aldosterone-producing adenoma (APA) (i.e. Conn's syndrome), unilateral or bilateral adrenal hyperplasia, or idiopathic hyperaldosteronism (IAH). Other rarer related conditions include familial hyperaldosteronism types I and II (2%) and an aldosterone-producing carcinoma (1–2%). [5]

The clinical picture of PHA tends to be non-specific. Some symptoms may result from hypokalemia, including fatigue, muscle weakness, constipation, paraesthesia, and arrhythmias. However, recent reports suggest that low serum potassium is a less frequent finding compared to past reports. The majority of

patients with PHA suffer from moderate to severe arterial hypertension, and are often resistant to antihypertensive treatment. Patients with PHA also suffer from cardiovascular events more frequently than other patients with hypertension. [6]

Successful PHA treatment requires identification of the sources of aldosterone overproduction. Unilateral overproduction of aldosterone is an indication that adrenalectomy should be considered. When successful, such treatment reduces the aldosterone hyperproduction, with a corresponding positive effect on hypertension, which can potentially result in the complete correction and normalization of hypokalemia. [7] On the other hand, patients presenting with IAH are treated with mineralocorticoid receptor antagonists since, in such cases, unilateral adrenalectomy does not result in improvement of clinical symptoms and bilateral adrenalectomy causes addisonism. [2]

Initial efforts to identify the source of aldosterone overproduction may include imaging methods, such as CT and MRI, however, these methods do not produce the most reliable results. Adenomas may evade detection because they are so small that they are below the resolution threshold. Moreover, adenomas can coexist with hyperplasia, and macronodular hyperplasia can mimic an adenoma. Another frequent finding is the presence of a hormonally inactive incidentaloma. [8] Adrenal venous sampling (AVS) is the best method for distinguishing unilateral and bilateral hypersecretion of aldosterone. [9, 10, 11]

In the present study, we aimed to evaluate the clinical and laboratory effects of adrenalectomy as a treatment for PHA. An additional goal was to identify parameters that predict the beneficial effects of surgery for hypertension treatment.

Materials And Methods

We performed a cross-sectional analysis of data from patients who had undergone adrenalectomy for PHA at the Department of Urology at the University Hospital in Olomouc, between January 2008 and December 2019. All patients were referred for surgery based on endocrinological, radiological, and surgical examinations. The patients received postoperative follow-up at an institutional endocrinology clinic. For this study, we analyzed the records of these patients. Written informed consent was obtained from the patients, and complete follow-up records were required for each patient's enrolment into the study.

Clinical and laboratory examinations

We initially identified patients with arterial hypertension who had not responded well to pharmacotherapy and who also had confirmed aldosterone overproduction. According to current guidelines, hypertension was defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg. In each case, both plasma renin activity (PRA) and serum aldosterone (ALD) were analyzed to determine the aldosterone-renin ratio (ARR). The normal ranges are 10–172 pg/mL for ALD, and 0.5–1.9 ng/mL/h for PRA. An ARR of > 30 indicated hyperaldosteronism. According to the guidelines, screening laboratory

tests were performed, with concomitant antihypertensive therapy (including with interfering drugs). [12, 13]

To confirm autonomous aldosterone overproduction, we performed a test in which 2000 mL of saline was infused over a 4-hour period after discontinuation of interfering medications in all patients who were able to tolerate such discontinuation (patients only took calcium channel blockers and alpha adrenoceptor blockers). To quantify the number of antihypertensive drugs, we estimated the daily defined dose (DDD) of antihypertensive medication, thus enabling standardised comparison of dosages between the drug classes. [14]

Radiological examination

All patients underwent radiological examination using computed tomography (CT) or magnetic resonance imaging (MRI). Regardless of radiological findings, all patients with primary hyperaldosteronism also underwent adrenal venous sampling without ACTH stimulation. The criteria for successful catheterisation included the identification of a higher concentration of cortisol in the adrenal vein compared to in the peripheral vein. Based on sufficiently selective sampling at our centre, we determined that the cortisol concentration in the adrenal vein compared to the peripheral vein should exhibit a ratio of greater than 2:1. Our criteria for successful lateralization were based on current valid recommendations. [12]

Aldosterone hypersecretion without ACTH stimulation was regarded as unilateral if the aldosterone/cortisol ratio on one side was over four times greater than the other side, i.e. the lateral aldosterone/cortisol ratio was over 4:1. A lateral aldosterone/cortisol ratio of below 3:1 was considered to indicate bilateral aldosterone hypersecretion. When the ratio was between 3:1 and 4:1, correct interpretation of the results required consideration of the clinical status and imaging findings, or a potential repetition of the test. In patients with a ratio of under 3:1 and a simultaneous finding of an adenoma with a diameter of > 3 cm, surgical intervention was indicated.

Surgical examination

Based on the results of endocrinological and radiological examinations, indications for unilateral adrenalectomy were established. Then the patients were evaluated by a urologist, to determine their operability. The surgeon also reviewed any previous abdominal surgeries, and the patient's general condition and BMI, before recommending appropriate surgery. The preferred surgery was a laparoscopic trans-peritoneal adrenalectomy. Retroperitoneal adrenalectomy was not considered as a primary approach, as this is not a preferred method within our department.

Postoperative follow-up

After surgery, patients underwent both clinical and laboratory examinations to evaluate their overall health status, blood pressure, potassium levels, PRA, ALD, and ARR. These evaluations were performed

with concomitant use of interfering medication, unless the drugs were discontinued due to cure or improvement of hypertension.

Statistical analysis

Analyses were performed using standard descriptive statistical methods. Continuous data were described as mean with standard deviation or median with 5–95 percentile range for continuous data, and categorical data as absolute and relative frequencies. Preoperative and postoperative characteristics of patients were compared using a paired Wilcoxon test. To assess possible differences between groups of patients according to their outcome, we used the Mann-Whitney U test for continuous variables, and Fisher's exact test for categorical variables. To evaluate the predictive power of patient characteristics in terms of the endpoint, we performed univariable and multivariable logistic regression, and the results are presented as odds ratio (OR), 95% confidence interval (CI), and statistical significance. A backward stepwise algorithm was used to select the optimal model, and the area under the ROC curve (AUC) was computed to evaluate the model's overall predictive power. Analyses were performed using SPSS V.25.0.0.1., and the level of statistical significance was set at $\alpha = 0.05$.

Results

Between January 2008 and December 2019, 87 patients with unilateral hyperaldosteronism underwent transperitoneal laparoscopic adrenalectomy. Table 1 presents the characteristics of these treated patients.

The clinical and laboratory outcomes of the surgeries were assessed after a median of 4 months (range, 1–82 month. In 45 patients (52%), the aldosterone-to-renin ratio was normalized after surgery, and these patients were regarded as "laboratory cured". An additional 21 patients (24%) did not require any antihypertensive drugs after surgery and were regarded as "clinically cured". Among the 66 patients who did not achieve clinically cured hypertension, 51 (77%) exhibited a reduction of DDD after surgery. Thus, in 72 (83%) of all enrolled patients, surgery had an overall positive effect on hypertension control. Table 2 presents the effects of surgery on selected parameters.

Table 3 shows the univariable analysis of predictors of successful treatment according to clinical results, based on the laboratory results presented in Table S1 (online supplement).

Multivariable logistic regression analysis revealed that clinical cure of hypertension was independently associated with female gender, absence of diabetes mellitus, and DDD < 4 (Table 4).

Discussion

One of the most important clinical outcomes in treatment of hyperaldosteronism is to control hypertension that is frequently severe and associated with end-organ damage. In the present study of patients who underwent adrenalectomy for hyperaldosteronism caused by unilateral hypersecretion of

aldosterone, we found that the main clinical outcome was better control of hypertension. Nevertheless, not all patients were able to discontinue their use of all antihypertensive medication after surgery. Uncured hypertension likely resulted from coexisting irreversible vascular changes that were induced by hypertension itself and/or by direct long-standing exposure to aldosterone. [15, 16]

In our cohort, 83% of surgically treated patients achieved hypertension control, as indicated by an overall reduction of DDD. Only 24% of patients achieved clinical cure (DDD of 0). Other published studies have described hypertension cure rates ranging between 15.3% and 55%, as defined by a blood pressure of < 140/90 mmHg without the use of antihypertensive drugs. [17, 18, 19, 20] Within our cohort, 59% of patients exhibited partial clinical success, with improved blood pressure control and reduction of DDD. Previous studies have shown that this important group includes an average of 47% of patients (range, 35–66%). [21]

The number of antihypertensive drug classes themselves does not accurately reflect the total consumption of antihypertensive drugs used to control blood pressure. Thus, the defined daily dose (DDD) has been adopted to enable analysis of the consumption of many prescribed, in the present study, antihypertensive drugs. [22] Use of the DDD allows clinicians to better counsel patients with primary aldosteronism regarding the predicted postoperative change in antihypertensive drug consumption. Our present investigation is one of only a few studies to adopt the DDD concept. [23] Antihypertensive therapy defined by the DDD was reduced from a DDD of 5.4 before to 3.0 after surgery, i.e. our cohort showed a mean postoperative decrease of 2.4 DDD.

A laparoscopic or retroperitoneoscopic approach is the surgical method of choice. Compared to open adrenalectomy, laparoscopic adrenalectomy is associated with shorter hospital stays and potentially fewer complications. [2] In this study, all patients were treated laparoscopically, and no serious adverse events were observed.

Previous studies have reported the following independent factors affecting the persistence of hypertension after adrenalectomy: male sex, advanced age, increased BMI, hypertension duration of > 6 years, preoperative use of > 3 types of antihypertensive drugs, and adrenal gland size. [24, 25, 26, 27, 28, 29, 30] Zarnegar et al. proposed a scoring system to predict the benefits of adrenalectomy for patients, which combines four independent factors: the number of antihypertensive medications used, BMI, hypertension duration, and female gender. [31]

In our study, hypertension reversal was independently associated with female gender, absence of diabetes mellitus, and use of less powerful antihypertensive treatment (DDD < 4). Notably, hypertension resolution or improvement was the most important clinical outcome of the surgery. Contrary, the most accurate indicator of successful surgical treatment was the change in ARR, which we found to be normalized in 71% of the participating patients.

In cases of hyperaldosteronism, adrenalectomy should only be indicated in cases with clearly demonstrated unilateral aldosterone hypersecretion. If the preoperative algorithm for localization of

hypersecretion exclusively relies on imaging methods, it is likely that up to 25% of patients will not be correctly identified. Our present data confirmed these findings, showing that 25.3% of our patients undergoing adrenalectomy had AVS-confirmed unilateral aldosterone secretion but had normal findings according to adrenal imaging. [11] AVS is the only method that can conclusively distinguish unilateral from bilateral aldosterone hypersecretion. Therefore, AVS is commonly considered a necessary prerequisite for adrenalectomy in all patients with primary hyperaldosteronism, regardless of the apparent findings on CT or MRI scans. [10, 12]

The importance of AVS appears to be particularly significant in elderly patients, who also show a greater incidence of non-functional adenomas. Additionally, young patients (age < 35 years), and cases of unilateral adrenal lesions with radiological features consistent with cortical adenoma seen on a CT scan, may not require AVS before proceeding to unilateral adrenalectomy. [12]

Notably, if both adrenal veins are not successfully catheterized, it may be necessary to repeat AVS, treat a patient medically, or consider surgery based on the findings of alternative diagnostic tests. [2] For 17 patients in the present study, we had to repeat AVS to obtain conclusive results.

Microscopic differentiation between an adenoma and adrenal hyperplasia may prove to be rather challenging. In cases of nodular hyperplasia, more nodules may be found, and the adrenal cortex surrounding these nodules will appear hyperplastic. In contrast, the histology of adenomas usually presents with extranodular atrophy. [32, 33] In our study, histological examinations were performed by several different histopathologists, therefore, it was practically impossible to clearly distinguish between the various forms of hyperplasia. Cortical adenoma can occur simultaneously with adrenal hyperplasia, but it has generally been reported that adrenal adenoma is the most common cause of unilateral aldosterone hypersecretion. However, a greater proportion of adrenal hyperplasia has been reported among patients with unilateral hypersecretion accurately diagnosed based on AVS. [34] In the present study, clinical outcomes were identical between patients with histological evidence of hyperplasia versus patients with evidence of an adenoma. This fact is consistent with studies that have reported unilateral adrenal hyperplasia to be far more frequent than previously thought. [35, 36, 37, 38, 39, 40]

A limitation of our present study is the small number of included patients, since the studied condition is rather rare. A strength of our study is the use of the DDD concept to enable analysis of the usage of combinations of multiple drugs.

Conclusions

Here we report outcomes of patients who underwent adrenalectomy for unilateral hyperaldosteronism indicated based on AVS. This study is one of only few investigations to adopt the DDD concept. Among surgically treated patients, 83% exhibited improved hypertension control, as shown by an overall reduction of DDD, while 24% achieved clinical cure (DDD of 0).

Declarations

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Conflicts of interests: None.

Availability of data and material: Yes.

Code availability: Not applicable.

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Tables

Table 1

Patients' characteristics (N = 87)

		n (% of N) or mean ± SD, median (5th–95th percentile)
Preoperative data		
Gender	Male	53 (60.9%)
	Female	34 (39.1%)
Age, years		57 ± 10, 57 (38–69)
Age, years	< 50	23 (26.4%)
	50–59	27 (31.0%)
	≥ 60	37 (42.5%)
BMI, kg/m^2		30.1 ± 5.0, 29.8 (22.2–39.5)
Coronary artery disease	Yes	8 (9.2%)
	No	79 (90.8%)
Diabetes mellitus	Yes	24 (27.6%)
	No	63 (72.4%)
Duration of hypertension, months		110 ± 83, 76 (22–240)
Duration of hypertension, years	< 5	32 (36.8%)
	5–9	29 (33.3%)
	≥ 10	26 (29.9%)
Systolic blood pressure, mmHg		163 ± 27, 160 (130–220)
Diastolic blood pressure, mmHg		95 ± 19, 95 (65–130)
Antihypertensive therapy, DDD		5.4 ± 2.6, 5.6 (2.0–10.4)
Serum aldosterone, pg/mL		724 ± 1,195, 287 (175–2 052)
Plasma renin, pg/mL		0.23 ± 0.34, 0.10 (0.05–0.64)
Aldosterone-to-renin ratio		562 ± 773, 311 (37–2,000)
Serum potassium level, mmol/L		3.24 ± 0.47, 3.20 (2.60–4.02)
Plasma sodium, mmol/L		141.4 ± 2.9, 141 (136–146)
Creatinine clearance, mL/s		1.30 ± 0.23, 1.39 (0.85–1.50)
Sampling ratio		7.4 ± 6.0, 5.0 (2.6–19.0)

Adrenalectomy side	Left	46 (52.9%)
	Right	41 (47.1%)
Imaging findings on surgery side	No findings	22 (25.3%)
	Adenoma	57 (65.5%)
	Hyperplasia	8 (9.2%)
Imaging findings on opposite side	No findings	69 (79.3%)
	Adenoma	12 (13.8%)
	Hyperplasia	6 (6.9%)
Operative data		
Histology	Adenoma	40 (46.0%)
	Hyperplasia	47 (54.0%)
Post-operative data		
Time post-surgery, months		14 ± 25, 4 (1–82)
Systolic blood pressure, mmHg		131 ± 17, 129 (105–160)
Diastolic blood pressure, mmHg		81 ± 11, 80 (65–100)
Antihypertensive therapy, DDD		3.0 ± 2.5, 3.0 (0.0–7.3)
Serum aldosterone, pg/mL		107 ± 78, 91 (10–239)
Plasma renin, pg/mL		1.84 ± 3.40, 0.64 (0.05–5.40)
Aldosterone-to-renin ratio		36 ± 77, 10 (1–141)
Serum potassium level, mmol/L		4.37 ± 0.45, 4.32 (3.65–5.23)
Plasma sodium, mmol/L		140.4 ± 3.0, 140 (136–145)
Creatinine clearance, mL/s		1.21 ± 0.32, 1.31 (0.63–1.50)

DDD, daily defined dose.

Table 2

Effects of surgery on selected parameters

	Preoperative	Postoperative	Difference	
	Mean ± SD	Mean ± SD	Mean ± SD	P
Systolic blood pressure, mmHg	163 ± 27	131 ± 17	−32 ± 32	<0.001
Diastolic blood pressure, mmHg	95 ± 19	81 ± 11	−14 ± 21	<0.001
Antihypertensive therapy, DDD	5.4 ± 2.6	3.0 ± 2.5	−2.4 ± 2.1	<0.001
Serum aldosterone, pg/mL	724 ± 1195	107 ± 78	−617 ± 1193	<0.001
Plasma renin, pg/mL	0.23 ± 0.34	1.84 ± 3.40	1.61 ± 3.43	<0.001
Aldosterone-to-renin ratio	562 ± 773	36 ± 77	−526 ± 767	<0.001

P values are from a paired Wilcoxon test.

DDD, daily defined dose.

Table 3

Univariable analysis of predictors associated with successful treatment of primary hyperaldosteronism based on clinical results

		Cured (n = 21)	Uncured (n = 66)	P
Gender	Male	6 (28.6%)	47 (71.2%)	**0.001**
	Female	15 (71.4%)	19 (28.8%)	
Age, years		52 ± 11	58 ± 9	**0.035**
Age, years	< 50	7 (33.3%)	16 (24.2%)	0.122
	50–59	9 (42.9%)	18 (27.3%)	
	≥ 60	5 (23.8%)	32 (48.5%)	
BMI, kg/m^2		28.1 ± 4.8	30.7 ± 4.9	**0.040**
Coronary artery disease	Yes	0 (0.0%)	8 (12.1%)	0.190
	No	21 (100.0%)	58 (87.9%)	
Diabetes mellitus	Yes	2 (9.5%)	22 (33.3%)	**0.048**
	No	19 (90.5%)	44 (66.7%)	
Duration of hypertension, months		63 (16–240)	80 (28–240)	0.168
Duration of hypertension, years	< 5	10 (47.6%)	22 (33.3%)	0.398
	5–9	7 (33.3%)	22 (33.3%)	
	≥ 10	4 (19.0%)	22 (33.3%)	
Systolic blood pressure, mmHg		157 ± 21	165 ± 29	0.346
Diastolic blood pressure, mmHg		96 ± 26	95 ± 16	0.908
Antihypertensive therapy, DDD		3.4 ± 2.1	6.0 ± 2.4	**< 0.001**
Serum aldosterone, pg/mL		291 (175–2551)	283 (181–2000)	0.491
Plasma renin, pg/mL		0.11 (0.05–1.10)	0.10 (0.05–0.62)	0.685
Aldosterone-to-renin ratio		296 (37–748)	313 (45–2,000)	0.425
Serum potassium level, mmol/L		3.29 ± 0.54	3.22 ± 0.45	0.512
Plasma sodium, mmol/L		140.5 ± 3.3	141.7 ± 2.7	0.072
Creatinine clearance, mL/s		1.42 (1.10–1.50)	1.33 (0.82–1.50)	0.260
Sampling ratio		5.0 (2.7–15.0)	5.0 (2.6–19.4)	0.874
Adrenalectomy side	Left	13 (61.9%)	33 (50.0%)	0.453

	Right	8 (38.1%)	33 (50.0%)	
Imaging finding on surgery side	No findings	1 (4.8%)	21 (31.8%)	**0.021**
	Adenoma	17 (81.0%)	40 (60.6%)	
	Hyperplasia	3 (14.3%)	5 (7.6%)	
Imaging finding on opposite side	No findings	17 (81.0%)	52 (78.8%)	0.999
	Adenoma	3 (14.3%)	9 (13.6%)	
	Hyperplasia	1 (4.8%)	5 (7.6%)	
Histology	Adenoma	13 (61.9%)	27 (40.9%)	0.131
	Hyperplasia	8 (38.1%)	39 (59.1%)	

Categorical variables are described using absolute and relative frequencies, quantitative normally distributed variables are presented as mean ± SD, and quantitative non-normally distributed variables are presented as median (5th–95th percentile).

P values were calculated using Fisher's exact test or the Mann-Whitney U test.

DDD, daily defined dose.

Table 4

Multivariable logistic regression model using a backward stepwise algorithm for selection of independent predictors of successful clinical cure of primary hyperaldosteronism

Predictor		OR (95% CI)	P
Gender	Male	Reference category	
	Female	6.17 (1.68; 22.61)	0.006
Diabetes mellitus	Yes	Reference category	
	No	6.34 (1.03; 38.96)	0.046
Antihypertensive therapy	DDD ≥ 4	Reference category	
	DDD < 4	10.62 (2.97; 37.94)	< 0.001

AUC (95% CI): 0.859 (0.761–0.957); P < 0.001; sensitivity, 85.7%, specificity, 72.7%.

DDD, daily defined dose.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TableS1.docx