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Original Article

Adrenalectomy improves hypertension control in patients with non-functional adrenal adenomas without causing endocrinological changes

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Abstract: Non-functional adrenal adenomas (NFAs) are associated with increased incidence of hypertension. The aim of this follow-up study was to assess the efficacy of adrenalectomy in the treatment of NFA patients with hypertension, and determine whether the surgical outcomes were associated with endocrinological changes. Between March 2002 and March 2013, 126 consecutive patients with NFA underwent adrenalectomy in our hospital. Of these, 90 (71.4%) individuals had preoperative hypertension, while 36 were normotensive. The patients with hypertension were reevaluated for blood pressure after a mean follow-up time of 59.2 (6-144) months. There were no statistically significant differences in clinical and endocrinological parameters between the hypertensive and normotensive groups. A total of 57/90 (63.3%) hypertensive patients showed hypertension control improvement after operation. However, there were no significant changes in endocrinological properties before and after operation, in both patient groups with improved and unimproved hypertension control. Multivariable analysis showed that age, pre-surgery hypertension grade, pre-surgery hypertension duration were significantly associated with an increased risk of non-effect after surgery in NFA patients ($P<0.05$). After adjusting age and pre-surgery antihypertensive medication, the RR value of pre-surgery hypertension grade was 2.525 (95% CI: 1.208-5.278), and the RR value of pre-surgery hypertension duration was 3.406 (95% CI: 1.257-9.226). These data suggested that adrenalectomy could be considered in NFA patients with hypertension, especially those with low hypertension grade and/or short hypertension course. Further studies are needed to clarify the underlying mechanisms.

Keywords: Hypertension, adrenalectomy, non-functional adrenal tumor

Introduction

Adrenal incidentalomas are clinically non-apparent adrenal masses discovered on radiological imaging performed for nonadrenal disease. The prevalence of adrenal incidentalomas is about 4% or higher prevalence rates that have been reported with the continued advances in imaging technology [1-4]. The vast majority of adrenal incidentalomas (in 70-80% of cases) are non-functioning adrenal adenomas (NFAs), which do not cause classical clinical signs and symptoms of hormone excess syndromes.

Despite NFAs being diagnosed as non-functioning during current routine laboratory hormonal evaluations, the prevalence of metabolic and cardiovascular disorders in NFA patients is significantly higher than the values obtained in health examination surveys of the general population [5-10]. Several adipocyte and endothelium derived cytokines, which are important markers of metabolic and cardiovascular alterations, were found to be higher in patients with NFA compared with healthy subjects [11, 12]. Interestingly, multiple reports have revealed some beneficial effects of adrenalectomy on metabolic and cardiovascular outcomes in NFA patients [13-15]. Based on these findings, adrenalectomy would be a valid therapeutic approach for NFA patients with metabolic and cardiovascular disorders. However, there is no consensus regarding the clinical management of this condition. The aim of the present study was to evaluate the effect of adrenalectomy on NFA patients with hypertension.

Materials and methods

Ethical statement

This study was approved by the Ethics Committee of Shandong Provincial Hospital (No. 2013-008).

Study participants

NFA patients surgically treated and regularly followed up at our hospital from March 2002 to March 2013 were included and retrospectively evaluated. All patients had undergone computed tomography scan to confirm diagnosis as well as detailed endocrinological examination before surgery. Diagnosis of NFA was based on the following criteria: no endocrinological abnormalities on clinical examination, hypertension (>140/90 mmHg) not considered to be specific symptoms of functional adrenal disease because of frequent presence in patients with adrenal incidentalomas; no abnormal laboratory findings, i.e. normal serum and urinary sodium and potassium levels; normal serum cortisol and ACTH levels; normal plasma aldosterone and renin activity (PRA); plasma aldosterone to PRA ratio lower than 20; normal 24 h urinary cortisol, 17-OHCS, 17-KS and catecholamine excretion. We specifically determined the necessary conditions as cortisol suppression below 1.8 μg/dl and >50% compared to baseline after 1 mg dexamethasone suppression test, excluding Subclinical Cushing's syndrome. We also only included the patients whose adrenal mass was definitely diagnosed as adrenocortical adenomas by postoperative histopathological studies.

NFAs were surgically treated because of one or more of the following causes: tumor size (≥4 cm); tumor size increasing during follow-up; patient wish for adrenal mass removal despite the medical advice that it could be benign. Although being advised that no consensus exists regarding the clinical management of NFA with hypertension, some patients still chose operation for possible improvement of hypertension control.

Study outcomes

Hypertensive patients were also classified according to the grades of hypertension [16]. The effect of adrenalectomy was evaluated in terms of hypertension control, and patients were categorized into three groups: 'complete effect', normotensive patients (systolic blood pressure ≤140 mmHg and diastolic blood pressure ≤90 mmHg) without further antihypertensive treatment; 'partial effect', patients administered reduced amounts of antihypertensive agents; and 'no effect', continued hypertension with the same amounts of antihypertensive agents or even more.

Data collection

In patients with hypertension, blood pressure was measured at baseline, and at 1 month, 6 months, 12 months, and 12-month intervals thereafter during the postoperative follow-up period; The preoperative (baseline) blood pressure was measured using standard sphygmomanometer and appropriately sized cuffs. Three readings of BP values with minimal intervals of 1 min were made with the patient in a seated position after resting for 5-10 min when was admitted into our hospital, and recorded the average value postoperative blood pressure values are those measured at the latest follow-up for each patient. All the original data were in the Supplementary Table.

Statistical analysis

Comparisons of continuous data were carried out using the Student's t or Mann-Whitney U test, and categorical variables were assessed with chi-square test. Multivariate unconditional logistic regression model based on the results of univariable analyses was performed to estimate the effects of pre-operative factors for blood pressure control. Relative risks (RRs) and 95% confidence intervals (CI) of pre-operative factors on post-operative effect were calculated in the multivariate model. The paired t-test was conducted to identify endocrological change before and after operation in the NFA patients.

All statistical tests were evaluated using a two-tail and a P value <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS 15.0 software (SPSS, Chicago, IL, USA).

Results

This study assessed 126 NFA patients, including 58 males and 68 females, averaging 51.6 years (range 14-76). A total of 90 (71.4%) patients had preoperative hypertension, while

Table 1. Main clinical and endocrinological features of the 126 patients with NFAs

	Normotensive (n=36)	Hypertension (n=90)	*t*	*P* value
Age	51.53±10.26	50.86±12.83	0.280	0.780
Gender			1.840	0.175
Male	20	38		
Female	16	52		
BMI (kg/m^2)	26.95±3.25	26.49±3.65	0.648	0.518
Sides			2.187	0.335
Left	15	47		
Right	16	37		
Bilateral	5	6		
Tumor size (cm)	3.13±1.23	2.85±1.22	1.175	0.242
Endocrinological findings				
Cortisol at 0800 h (μg/dl)	13.56±3.28	14.54±2.70	1.730	0.086
Cortisol at 1800 h (μg/dl)	7.34±1.73	7.90±1.83	1.568	0.119
Post-DST Cortisol 0800 h (μg/dl)	1.02±0.29	1.09±0.32	1.099	0.274
ACTH at 0800 h (pmol/L)	4.10±1.69	4.00±1.47	0.331	0.741
Aldosterone 0800 h (ng/dl)	16.29±7.05	17.35±7.04	0.763	0.447
PRA (ng/ml/h)	0.97±0.65	1.18±0.49	1.755	0.085

36 were normotensive. The main clinical and endocrinological features of these patients are summarized in **Table 1**. There were no statistically significant differences in clinical or endocrinological values between the hypertensive and normotensive groups.

All patients had total or partial adrenalectomy, performed by trans- or retroperitoneal laparoscopic operation, with only those with multiple adrenal nodules administered total adrenalectomy. For patients with bilateral disease (eleven), bilateral adrenal masses were removed by one-stage bilateral partial adrenalectomy (only adrenal tumors resected). The tumors were 62 and 53 on the left and right sides, respectively, while 11 were bilaterally located. The tumor diameters were 2.93±1.22 cm. In all cases, tumor histology indicated benign adrenocortical adenoma; in 7 cases adrenocortical adenomas had concomitant nodular hyperplasia. All adrenalectomies were successfully performed without major complications, and no patients needed hydrocortisone substitution after the operation.

For the 90 patients with hypertension, blood pressure was routinely measured during follow-up, and mean follow-up duration was 59.2 (6-144) months. Adrenalectomy cured hypertension in 39 patients (43.3%), with 'complete effect'; meanwhile, 18 (20%) patients had persistent hypertension, which was much easier to control ('partial effect'); thus, 57 (63.3%) patients altogether obtained improvement of blood pressure control after adrenalectomy. The remaining 33 patients had continued poor blood pressure control ('no effect'). The effect (complete and partial) and non-effect patient groups were compared for main clinical and endocrinological features (**Table 2**). The differences in mean cortisol, ACTH, aldosterone and PRA levels were not significant between the effect and no-effect groups ($P>0.05$).

Postoperative levels of serum cortisol at 08:00 h and plasma aldosterone and PRA were measured at first follow-up (1 month after operation), and the values were relatively lower compared with preoperative baselines, either in effect or no-effect groups, but with no statistically significant differences ($P>0.05$). Postoperative Post-DST cortisol levels at 08:00 h were also similar to preoperative baseline values (**Table 3**).

As shown in **Table 2**, mean age (48.7 years) in the effect group was significantly lower compared with the no-effect group (54.6 years) ($P<0.05$); a similar trend was obtained for mean preoperative systolic blood pressure, with 164.96 mmHg and 173.12 mmHg obtained for the effect and no-effect groups, respectively ($P<0.01$); mean preoperative diastolic blood pressure (101.26 mmHg) was slightly lower than that in the no-effect group (103.79 mmHg), but the difference was not statistically significant ($P>0.05$). Fewer pre-operative antihypertensive agents were administered in the effect group (1.56) compared with the no-effect group (1.91), with a statistically significant difference ($P<0.05$). The mean number of post-operative

Table 2. Main clinical and endocrinological features of patients with hypertension

Variables	No effect group (n=33)	Effect group (n=57)	*t*	*P* value
Age (years)	54.64±11.17	48.67±13.31	2.170	0.033
Sex			1.845	0.174
Male	17	21		
Female	16	36		
BMI (kg/m^2)	27.09±3.75	26.11±3.68	1.216	0.227
Pre-surgery SBP (mmHg)	173.12±12.87	164.96±14.44	2.684	0.009
Pre-surgery DBP (mmHg)	103.79±6.72	101.26±7.94	1.535	0.128
Pre-surgery hypertension grade			2.822	0.005
Grade 1	2	20		
Grade 2	11	18		
Grade 3	20	19		
Pre-surgery hypertension duration (year)			9.029	0.003
<5 years	10	36		
≥5 years	23	21		
Pre-surgery antihypertensive medication	1.91±0.81	1.56±0.57	2.395	0.019
Post-surgery antihypertensive medication	2.12±0.78	0.32±0.47	13.724	<0.001
Post-surgery SBP (mmHg)	168.70±10.39	133.98±12.91	13.169	<0.001
Post-surgery DBP (mmHg)	100.91±7.85	86.40±7.48	8.709	<0.001
Sides			0.120	0.942
Left	18	29		
Right	13	24		
Bilateral	2	4		
Tumor size (cm)	2.83±1.07	2.86±1.31	0.039	0.969
Pre-surgery Endocrinological findings				
Cortisol 0800 h (μg/dl)	14.05±2.40	14.82±2.83	1.318	0.191
Cortisol 1800 h (μg/dl)	7.80±1.59	7.95±1.97	0.397	0.692
Post-DST Cortisol 0800 h (μg/dl)	1.04±0.30	1.11±0.34	0.959	0.340
ACTH 0800 h (pmol/L)	4.21±1.73	3.95±1.30	0.764	0.448
Aldosterone 0800 h (ng/dl)	16.67±6.93	17.74±7.13	0.691	0.491
PRA 0800 h (ng/ml/h)	1.20±0.52	1.16±0.47	0.396	0.693

antihypertensive agents in the effect group was significantly reduced to 0.32 (P<0.001), while the change in the no-effect group postoperatively was not statistically significant. The effectiveness of adrenalectomy was also evaluated according to the grades of hypertension. The effective rates for grades 1, 2 and 3 were 90.9% (20/22), 62.1% (18/29) and 48.7% (19/39), respectively; the difference between grades 1 and 2 hypertension groups was significant (P<0.05); idem for grades 1 and 3 groups (P<0.01); however, the difference between grades 2 and 3 was not statistically significant (P>0.05). The median preoperative hypertension duration in the effect group was 12 months, significantly lower than that of the no-effect group (54 months) (P<0.01); in 46 patients with hypertension lasting less than 5 years, 36 (78.3%) showed a positive response to adrenalectomy, while in the remaining 44 patients with hypertension duration ≥5 years, only 21 (47.7%) showed a positive response, indicating a statistically significant difference (P<0.01). After univariate analysis, age, pre-surgery SBP, pre-surgery hypertension grade, pre-surgery hypertension duration, pre-surgery antihypertensive medication, post-surgery antihypertensive medication, post-surgery SBP, and post-surgery DBP were significantly different between the effect and no effect groups (P<0.05). We chose 4 variables (i.e. age, pre-surgery hypertension grade, pre-surgery hypertension duration, pre-surgery antihypertensive medication) to assess effects for non-effect

Table 3. levels of cortisol and aldosterone in hypertension patients before and after operation

Variables	No effect group (n=33)				Effect group (n=57)			
	Preoperative	Postoperative	*t*	*P*	Preoperative	Postoperative	*t*	*P*
Cortisol at 0800 h (μg/dl)	14.05±2.40	13.94±2.23	1.345	0.188	14.82±2.83	14.70±2.79	1.724	0.090
Post-DST Cortisol at 0800 h (μg/dl)	1.04±0.30	1.03±0.31	1.128	0.268	1.11±0.34	1.10±0.34	1.345	0.184
Aldosterone at 0800 h (ng/dl)	16.67±6.93	16.33±6.45	1.036	0.308	17.74±7.13	17.65±7.00	1.893	0.064
PRA 0800 h (ng/ml/h)	1.20±0.52	1.19±0.53	1.666	0.105	1.16±0.47	1.14±0.47	1.825	0.073

Table 4. Parameters from logistic regression model for hypertension control

Variables	β	*SE*	Wald χ^2	df	*P*	*RR*	95% CI for *RR*	
							Lower	Upper
Age	0.049	0.023	4.487	1	0.034	1.050	1.004	1.098
Pre-surgery hypertension grade	0.926	0.376	6.059	1	0.014	2.525	1.208	5.278
Pre-surgery hypertension duration	1.225	0.508	5.809	1	0.016	3.406	1.257	9.226
Pre-surgery antihypertensive medication	0.361	0.418	0.746	1	0.388	1.435	0.632	3.256
Constant	-7.687	1.909	16.212	1	0.000	0.000	-	-

SE, standard error; df, degree of free; *OR*, odds ratio; CI, confidence intervals.

after surgery in NFA patients by unconditional logistic regression analysis. Parameters estimates and test results of multifactorial logistic models are presented in **Table 4**. Multivariable analysis showed that age, pre-surgery hypertension grade, pre-surgery hypertension duration were significantly associated with an increased risk of non-effect after surgery in NFA patients ($P<0.05$). After adjusting age and pre-surgery antihypertensive medication, the RR value of pre-surgery hypertension grade was 2.525 (95% CI: 1.208-5.278), and the RR value of pre-surgery hypertension duration was 3.406 (95% CI: 1.257-9.226).

Discussion

Previous studies have shown that hypertension frequency ranges from 20 to 82% in NFAs patients [6-10]; in the majority of these studies hypertension frequency was higher than prevalence rates obtained from health examination surveys of the general population. The prevalence of hypertension was 71.4% in the present study. The probable explanation for the relatively high rate is that in some cases ultrasonography or computer tomography was performed preferably in hypertensive patients to determine secondary causes.

The therapeutic choice in NFA still fuels debates. Several reports have assessed the effects of surgical removal on metabolic and cardiovascular outcomes, including hypertension control in patients with NFA. Bernini et al. revealed improved blood pressure in 9 NFA patients [13]. In addition, Chiodini et al. showed improvement of blood pressure in 9 of 30 NFA patients [14]. Izaki et al. demonstrated blood pressure reduction in 7/11 NFA patients with preoperative hypertension [15]. Despite the positive findings, the main concern in these studies was their small sample sizes. Sereg et al evaluated 125 individuals (112 NFA and 13 Subclinical Cushing's syndrome), and adrenalectomy was performed in 47 cases but failed to reduce the prevalence of various adverse vascular events, including hypertension [10].

In the present study, the effect of adrenalectomy was evaluated in 90 NFA patients with hypertension, and 63.3% individuals showed improvement in hypertension. The patients requiring less pre-operative antihypertensive agents to control hypertension responded better compared with those in need of more preoperative antihypertensive agents. Moreover, patients with grade 1 hypertension had a much better response than those with grade 2 or 3 hypertension. These data suggested that the effects of NFAs on blood pressure might be weak; thus, low grade hypertension was more likely associated with NFAs. As shown above, patients who did not respond to adrenalectomy were older than those positively responding; in addition, longer hypertension duration was associated with no response to adrenalectomy. In studies assessing primary aldosteronism,

patients aged 50 years or younger with less than 5 years of hypertension were more likely to become normotensive after adrenalectomy [16, 17]. Irreversible vascular damage has been suggested as the primary reason why prolonged hypertension constitutes a risk factor for surgical outcome.

The association between NFA and unfavorable metabolic and cardiovascular status remains unclear. Several evidences have suggested that glucocorticoid secretion from NFA is subtle and below the detection limit of current laboratory facilities. An *in-vitro* study showed that steroid production from hormonally inactive adrenocortical tumors is not overtly different from that of hormone active tumors. In addition, cortisol secretion from NFA varies markedly compared to normal adrenal glands, suggesting that cortisol autonomy might exist in even clinically and hormonally silent adrenal adenomas [18]. Studies have demonstrated that NP-59 scintigraphy can reveal steroid accumulation in NFAs, suggesting steroidogenesis in these tumors [19, 20]. Previous studies also observed that patients with NFA show cortisol elevation in post dexamethasone suppression test (not exceeding the cut-off; 1.8 μg/dl), and reduced dehydroepiandrosterone sulfate levels (not below the cut-off, 40 μg/dl) compared with age and BMI matched healthy controls. These findings might reflect the subtle alterations in glucocorticoid production in NFA patients [21-23]. We found no significant differences in cortisol and aldosterone levels between NFA patients with and without hypertension, or between hypertensive patients with and without response to surgical treatment. In addition, we obtained no significantly decreased levels of cortisol and aldosterone in NFA patients after surgery. However, our negative endocrinological data also support the idea that hormone production in NFAs could be subtle, and may not be detected by current laboratory techniques.

In conclusion, the indication of adrenalectomy for non-functional adrenal incidentalomas is generally considered for lesions more than 4-6 cm. our data support that surgical adrenalectomy could be considered in NFA patients with hypertension, especially those with low hypertension grade and/or short duration of disease course. However, the underlying mechanisms need further studies.

Disclosure of conflict of interest

None.

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