J. Endocrinol. Invest. 32: 57-62, 2009

Long-term results of laparoscopic adrenalectomy for primary aldosteronism

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ABSTRACT. ***Background:*** **The management of primary aldosteronism is currently achieved by both medical and surgical treatment. Laparoscopy has in recent years unquestionably become the gold standard in adrenal surgery for benign lesions. This study aims to evaluate our clinical results among patients who underwent laparoscopic adrenalectomy (LA) for primary aldosteronism.** ***Methods:*** **From January 1994 to January 2006, amid LA series, 59 primary aldosteronism patients were treated in our institution. Patients were 33 males and 26 females with mean age 49.3 yr (19-78). The mean body mass index was 25.9 kg/m^2 (20.5-33.3). The mean size of lesion was 2.9 cm (1-5.5). Clinical symptoms were as follows: hypertension and symptomatic/asymptomatic hypokalemia (54), hypokalemia (5).** ***Results:*** **Thirty-five left and 24 right LA were performed. On the left side, 22 procedures were carried out by anterior approach, 9 by anterior submesocolic route, and 4 by means of flank approach. All right procedures were completed by the anterior supine approach. The mean operative time was 103.5 min for left and 92.8 min for right adrenalectomy. There was one major complication, a colonic post-operative fistula, regarding a left adrenalectomy case. The mean post-operative hospital stay was 3 days (1-9). The cure rate of hypertension and hypokalemia was similar to the current literature results.** ***Conclusions:*** **LA is a safe and effective option in the treatment of primary aldosteronism. Appropriate selection of patients, larger adrenal masses and duration of symptoms are determining factors in the success rate of hypertension management.**
(J. Endocrinol. Invest. 32: 57-62, 2009)

INTRODUCTION

Hypertension represents a growing problem in western countries. In Europe and in the United States roughly 25-30% of people are estimated to be hypertensive (1). When investigating the etiology of hypertension, secondary hypertension may be found which may be managed by surgical therapy. In 1955, Conn described a syndrome characterized by hypertension, hypokalemia, and suppressed plasma renin activity due to an excessive secretion of the hormone aldosterone into the blood from an abnormal adrenal gland (2). This condition, namely primary aldosteronism, previously thought to occur in few cases, is now the object of greater interest, following the refinement of hormonal tests and imaging tools. The prevalence of primary aldosteronism amongst hypertensive patients is approximately 6-7%. Usually, primary aldosteronism is investigated and diagnosed through 3 levels of study: screening, confirmatory, and subtype differentiation studies. Kalemia, plasma aldosterone concentration (PAC), plasma renin activity (PRA) and PAC:PRA ratio are the mandatory first-level screening tests. A PRA<1 ng/ml per h, a PAC:PRA ratio >20 ng/dl per ng/ml per h and a PAC>415 pmol/l (ng/dl) are highly indicative of primary aldosteromism, taking into account that a significant number of hypertensive patients with primary aldosteronism is normokalemic or sub-clinically hypokalemic. After this first diagnostic step, the suspected primary aldosteronism is further investigated by using confirmatory tests, as iv saline loading, oral sodium loading or fludrocortisone suppression test (3). Essentially, two types of abnormality of the adrenal gland are observed: adenoma, usually monolateral, and hyperplasia, generally bilateral. An aldosterone-producing adenoma (APA) is a common cause of surgically correctable hypertension, while bilateral idiopathic adrenal hyperplasia (IAH) is treated with medical therapy, such as spironolactone (1, 4, 5, 6). Since this is a completely different treatment, it is of paramount importance to achieve differential diagnosis between APA and IAH (7). Concerning this, postural studies have demonstrated a significantly higher increase of PAC value from supine position to ambulation in subjects with IAH rather than in patients affected by APA, in which PAC could even decrease (8, 9). Bilateral adrenal vein sampling, first described in 1969 (10), is nowadays a basic procedure in searching for a lateralization of aldosterone production, APA or monolateral hyperplasia, in patients with primary aldosteronism, independently of computed tomography (CT) scan or magnetic resonance imaging (MRI) results, since its sensitivity approaches 100% with a positive predictive value of 90% (11). Moreover, despite being uncommon, there are some uncommon subtypes of hyperaldosteronism which are usually medically correctable. Glucocorticoid remediable aldosteronism (GRA), is a rare, autosomal dominant form of hypertension affecting young adults with a history of familial hypertension hypokalemia-associated, in which aldosterone production comes under regulatory control of ACTH due to a fusion gene (12). A further, rare condition occurring in often normokalemic patients is the renin-responsive adrenocortical adenoma. Patients with a unilat-

Key-words: Adrenal tumors, laparoscopic adrenalectomy, minimally invasive surgery.

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Accepted June 9, 2008.

eral source of hyperaldosteronism, adenoma or hyperplasia, as well as selected cases of adrenal carcinoma, may be successfully treated by adrenalectomy (9, 13). Laparoscopic adrenalectomy (LA), is to date the gold standard for benign adrenal lesions (14-18) since Gagner in 1992 reported the first procedure. The cure rate of primary aldosteronism by means of LA may be up to 50-60% depending on many factors (19-23). The present study aimed to evaluate the clinical outcome of a cohort of patients who underwent LA for APA or selected IAH.

MATERIALS AND METHODS

Patients

From January 1994 to January 2006, 246 LA were performed in our department. Among these, 59 procedures were carried out for primary aldosteronism. Patients were 33 males and 26 females with mean age 49.3 yr (19-78), and mean body mass index 25.9 kg/m^2 (20.5-33.3). All patients were previously referred for the screening to the endocrinologist, being affected by one or more conditions: hypokalemia, including diuretic-induced hypokalemia, resistant hypertension despite therapy. Patients were investigated and asked to report any other symptoms, such as weakness, fatigue or headache. Finally, there were 54 patients with hypertension and clinical/sub-clinical hypokalemia (91.5%) and 5 with hypokalemia (8.5%) (Table 1). Family history of hypertension, preoperative therapy, and number of drugs and renal function were investigated as well. The drugs taken depended on blood tests and symptoms, i.e. hypertension and hypokalemia or cramps, and were as follows: mineralocorticoid receptor antagonist, such as spironolactone, in association or not with anti-hypertensive agents, alpha blockers, in one drug, or combination two/three drugs therapy. Twenty-nine patients (49%) had one-drug pre-operative therapy, while the remaining assumed additional anti-hypertensive medications in addition to spironolactone. The latter was taken by 53 patients (89.8%) on the whole.

Pre-operative assessments

All patients were preliminarily recommended to stop their medications for two-three weeks at least (wash-out), in order to avoid inaccurate results. Having determined the kalemia, PAC, PRA, and PAC:PRA ratio, patients underwent iv saline loading as confirmatory test. Diagnosis between APA and IAH was carried out by means of PAC supine/upright and adrenal vein sampling. This latter was routinely performed in patients with primary aldosteronism starting from 2003. Usually a percutaneous transfemoral approach was used for adrenal vein sampling, and samples of venous blood were collected from the left adrenal vein, the right adrenal vein and from the lower inferior vena cava for aldosterone and cortisol measurement. The cannulation of the adrenal veins is assumed if cortisol levels are doubled in the adrenal vein samples compared with the lower sample. The main difficulty with the technique is the failure to catheterize the right adrenal vein, which occurs in 10-30% of cases (24) as reported in the literature and as we observed in our experience. There is no standard cut-off level for the success of lateralisation. However, a ratio of at least 2 between cortisol levels in the adrenal vein and peripheral vein is accepted, and we used this cut-off. In the broadest sense, the lateralization criteria we used beyond the aldosterone/cortisol ratios by venous sampling, looking to determine a dominant side of aldosterone production along with contralateral suppression, included the imaging evidence of adrenal nodules or masses. In the presence of a vein sampling failure or an uncertain cut-off, the positive imaging result was in itself advising for adrenalectomy. In our experience the adrenal venous sampling suggested excluding from surgery 9 patients with a well-grounded suspect of IAH, while in 32 cases the diagnosis of surgically correctable primary aldosteronism was achieved. The dexamethasone 4-day suppression test (DSH) was performed in order to exclude GRA in 3 cases, in which the aldosterone levels fell by 50% approximately and thereafter, by the end of test, returned to the previous levels. This result suggested excluding GRA and the patients were not further investigated with genetic tests that otherwise would have been required, since DSH displays a low specificity to rule out GRA. Before surgery, all patients underwent an imaging work-up consisting of ultrasound, CT scan and/or MRI. The mean size of lesions found was 2.9 cm (1-5.5) (Table 1). The duration of hypertension was included in predictors of persistent hypertension after surgery, and this was approximately 47 months, with a wide range (18-92). In this way, patients undergoing LA for Conn's adenoma were divided into 4 groups: 8 hypertensive for less than 5 yr, 24 for 10 yr, 15 for 20 yr, and 8 more than 20 yr. Preoperative assessments results are reported in Table 2.

Table 1 - *Data and symptoms of patients.*

Sex (M *vs* F)	33 *vs* 26
Mean age, yr (range)	49.3 (19-78)
Mean BMI (range)	25.9 (20.5-33.3)
Mean size of lesion cm (range)	2.9 (1-5.5)
Symptoms	
-hypertension and sympt./asympt. hypokalemia (no.)	54
-hypokalemia (no.)	5

BMI: body mass index; M: males; F: females.

Operative technique

Concerning LA, there are many studies providing an exhaustive and detailed description of the surgical technique, as well as debating over the best route to reach the adrenal gland: anterior, lateral or posterior way (18, 25-28). Indeed, this comparison will not be debated here, and we limit our description to a very brief summary of anterior submesocolic route that we first reported in 2005. From the start of LA, our preferred choice was toward the supine anterior trans-peritoneal route, even if later-

Table 2 - *Laboratory data before surgery.*

	Mean	Normal range
Serum potassium (mmol/l)	2.4 (1.4-3.1)	3.6-5.0
Urinary potassium (mmol/24 h)	51 (29-110)	15-44
Plasma renin upright (ng/ml/h)	0.878 (0.650-2.125)	>1
Plasma aldosterone upright (pmol/l)	1221 (350-2980)	100-800
Plasma aldosterone supine (pmol/l)	1320 (550-3650)	25-400
Urinary aldosterone (nmol/24 h)	106 (31-310)	17-70
Plasma aldosterone/renin activity ratio	27 (9.7-123)	<20

al flank intra-peritoneal and posterior extra-peritoneal approaches have been employed in selected cases.

Submesocolic route for left LA

This approach allows the removal of left adrenal lesions up to 6-7 cm. Since this route permits the preliminary ligature of adrenal vein, it could be preferred in adrenal pheochromocytoma removal. Technically, the root of transverse colon is raised and the Treitz ligament and inferior mesenteric vein (IMV), at inferior pancreatic margin, are identified. Laterally to IMV at this point, the peritoneum of mesocolon root is divided and the pancreatic body gently lifted up. By few dissection manoeuvres, or immediately in a thin patient, left adrenal vein is visualized and closed. Thereafter the adrenalectomy is carried out. Short operative time (OpT), minimal tissue dissection, and very low blood loss are the main advantages of this route.

Statistics

Statistical analysis included the paired Student t-test. A probability value <0.05 was interpreted to denote statistical significance, assuming alpha set at 0.05; and power =80%. Box Plot graphical displays blood pressure trend based upon the years of disease. Univariate analysis of factors involved in blood pressure after surgery, such as age and duration, adjusted for BP before surgery was carried out. The Primer of biostatistics for Window software (McGraw-Hill, Blacklick, Ohio, USA) was used.

RESULTS

In all cases, adrenalectomy was completed by laparoscopy. Left adrenalectomy was performed by flank approach in 4 cases, submesocolic route in 9 cases and anterior approach in 22 patients. All 24 right adrenalectomies were carried out in the anterior supine position. Mean overall OpT was 103.5 min [45-180] in left adrenalectomy, and 92.8 min [30-155] in right adrenalectomy. Evaluating left OpT by access route, the submesocolic way required a mean OpT 68.3 min [45-90], the anterior route 112.1 min [45-180], and the flank approached a mean OpT 137.5 min [80-180]. Associated procedures were done in 3 patients: cholecystectomy [2], during an anterior right and left adrenalectomy, and ovariectomy [1] during a right adrenalectomy. A major complication occurred intra-operatively, in spite of its post-operative detection, consisting in a colonic splenic flexure lesion while performing a left LA by supine position, at the beginning of the series. A left hypochondrium abscess (3×5 cm) with fever and leucocitosis occurred in this patient. This complication was successfully treated by means of percutaneous ultrasound-guided drainage, antibiotic, and fast. No intra- or post-operative blood transfusions were administered. Patients were ambulating freely and tolerating the oral intake within 24 h after surgery. No post-operative major complications or mortality were observed. Mean hospital stay was 3 days [1-9]. Histology revealed APA in 53 and adrenal hyperplasia in 6 cases. In detail, there were a solitary cortical adenoma in 49 cases (83%), a cortical nodule adenoma amid adrenocortical hyperplasia in 4 cases (6.9%), and unilateral adrenal hyperplasia in 6 patients (10.1%).

Follow-up

After the hospital discharge, patients were followed up with periodical checks, in person or by telephone. Seven patients were lost after a mean 10-month follow-up and 2 patients died for unrelated causes. Finally, 50 patients received a mean 48-month [20-128] follow-up. Systolic and diastolic blood pressure, potassium levels and anti-hypertensive therapy were evaluated. Mean blood pressure level at discharge was 145/90 mmHg, remarkably lower (p<0.05) if compared to the mean pre-operative value (180/108 mmHg). In Figure 1, the blood pressure measurements before and at least 12 months after surgery are reported. In all cases adrenal removal resulted in a decrease of blood pressure. Hypertension was cured (systolic not exceeding 140 mmHg) in 21 cases (38.8%) stopping any medication, and partially cured (systolic not exceeding 140 mmHg with reduced anti-hypertensive drug therapy) in 26 patients (48%). In 7 patients (12.9%) blood pressure did not significantly respond to adrenalectomy. Univariate analysis of factors evaluated for an association with the cure of hypertension, or the improvement of blood pressure, was focused on: duration of hypertension, patient age, sex, family history of hypertension, and pre-operative therapy with fewer than 3 drugs. The cure rate evaluating each factor was: hypertension duration,

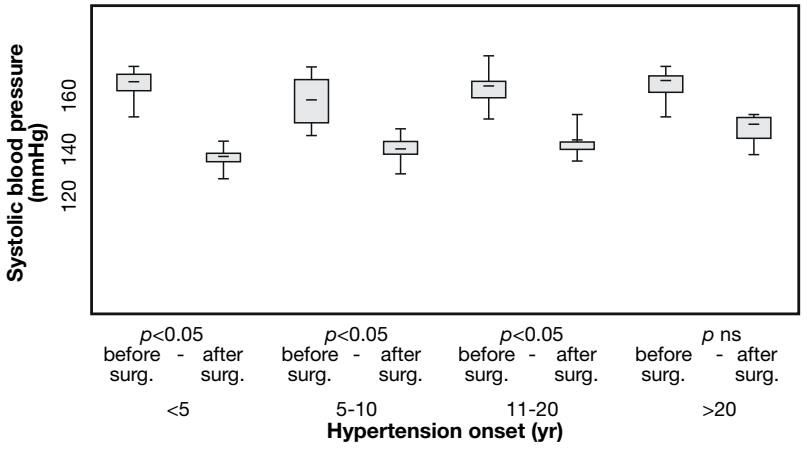

Fig. 1 - *Box Plot analysis of blood pressure before/after surgery, based on hypertension duration before surgery (4 groups).* p *was non significant in patients hypertensive for more than 20 yr.*

34 patients (66.6%) <10 yr *vs* 18 (33.4%) >10 yr ($p<0.05$), patient age 38 (71.4%) <50 yr old *vs* 16 (28.6%) >50 yr old ($p<0.001$), sex 29 males (27.5%) *vs* 25 females (72.5%) ($p<0.001$). Concerning the group of hypertension improvement with reduced therapy, the result depended on duration of disease only, 59% <10 yr *vs* 41% >10 yr ($p<0.05$), while age and sex were not statistically significant (Table 3). All patients became normokalemic.

DISCUSSION

Primary aldosteronism is a term describing disorders associated with abnormal aldosterone excess related to the renin-angiotension system. This laboratory finding corresponds more often with hypertension and, less often, hypokalemia. Nonetheless, the investigation for primary aldosteronism limited to patients having a low blood potassium and in whom blood pressure is moderately to severely elevated (>160/110 mmHg) often controlled by medication with difficulty, may be misleading. For instance, up to 30-40% of patients with proven Conn's syndrome have normal blood potassium levels. On the other hand, a significant proportion of patients with hypokalemia have no symptoms. These patients may manifest aspecific signs or symptoms related to the severity of low potassium levels, in turn partly related to sodium intake, and despite being questioned about a past history of muscle weakness, polyuria and or polydipsia, highly suggestive of Conn, it is not surprising that their primary aldosteronism was treated for a long time as essential hypertension. Primary aldosteronism, the most common form of endocrine hypertension, has an estimated peak age of distribution among the 3rd and 5th decades. Usually, the adrenal lesion responsible for primary aldosteronism is a solitary APA. The most rigorous method of diagnosis is to measure the blood levels of the two hormones aldosterone and renin. In Conn's syndrome, the aldosterone level is elevated and the renin level is low or undetectable. The aldosterone:renin ratio is accepted almost universally as one of the most reliable screening tools, despite some caution about its systematic use (9, 29). The increased interest over this syndrome is justified because primary aldosteronism is the main curable cause of secondary hypertension, with a significant success rate in clinical symptoms control. A keystone among the issues involved in screening this condition is represented by the differentiation of the adenoma from hyperplasia. In fact, only adrenalectomy for adenoma allows good results, as well as adrenal removal based on one side hyperplasia. When no lateralization is found, patients are treated as having bilateral hyperplasia, undergoing medical therapy (10). The refinement and increasing use of screening and diagnostic tests, involving both imaging and laboratory, has in recent years improved the accuracy of diagnosis of primary aldosteronism in hypertensive patients. Concerning this, there are several epidemiologic studies investigating the prevalence of primary aldosteronism. In 2003, Mosso reported an increasing prevalence of Conn based on hypertension stage, starting from 2% of hypertensive stage I patients to 13% in stage III hypertension (30). Besides, amid patients suffering from resistant hypertension, the prevalence of primary aldosteronism by some authors has been reported to be up to 20% (1, 29). Based on these epidemiological appraisals, since approximately 60 million people live in Italy, several hundred thousand hypertensive patients might have Conn and, as a consequence, the potential to cure this condition by surgical excision. This may explain the rising interest of both endocrinologists and surgeons in this entity/syndrome. LA was first described in the literature in 1992 and progressively expanded its role until becoming the preferred procedure for adrenal gland removal. The benefits of the minimally invasive approach are universally known as shorter hospitalization, more rapid return to work, better cosmetic results and patient satisfaction. Also, post-operative ileus, hernias, and adhesions incidence support laparoscopy. Combination of these factors led to investigate both indications to surgery and percentage of patients undergoing LA for primary aldosteromism. In 2005, Chavez-Rodriguez and coll. divided their series of adrenalectomies in two groups: before and after the introduction of laparoscopy. As expected, no change was observed in terms of indications for adrenalectomy, but patients having primary aldosteronism were referred to laparoscopy in higher percentages than previously were referred to laparotomy (15). LA is performed by lateral transperitoneal route in about 80% of published cases (19, 8, 31-33) despite the "ideal approach", meant as a tailored approach, based on patient and lesion features, which can be defined as a still open debate. Anatomical landmarks and chronological sequence of surgical steps are invoked or denied by surgeons having different points of view. For instance, during right LA, the identification of the lateral margin of the inferior cava vein, rapidly leading to the identification of both the medial margin of the adrenal gland and the visualization of the adrenal vein, proves easier in a supine patient approached anteriorly rather than in the flank-lateral (25). On the other hand, authors supporting flank lateral approach affirm that the simple position-gravity, in a patient 90° flank rotated, allows the achievement of the adrenal gland with a minimal or absent viscera dissecting manoeuvres (16). Moreover, studies have reported recommending as early as possible adrenal vein ligature, especially facing adrenal pheochromocytoma, since in spite of an adequate pre-operative therapy, the gland manipulation may have complications (3, 24); others have denied that early or otherwise vein ligature is a real problem (20, 31, 35, 36). Anyway, the recent improvements of laparoscopy, as left adrenalectomy by submesocolic way with less dissection, early adrenal

Table 3 - *Cured* vs *persistent hypertension related factors at univariate analysis.*

Factors	Cure of hypertension		*p*
	Yes (21)	No (26)	(Univariate analysis)
Sex (female)	14	10	<0.05
Age (yr)	43.3	59.3	<0.001
Duration (yr)	7.6 (<1-14)	13.4 (2-28)	<0.001
Pre-operative therapy two or less drugs	15	8	<0.001
No family history of hypertension	18	12	<0.05

vein ligature and decreased operative time, represent nothing but the effort to further minimize surgery (28). Apart from operative technical details, since the aim leading the analysis of the present series is focused on long-term results on LA for primary aldosteronism, we can draw the following remarks: assuming each patient is correctly evaluated before surgery, LA normalizes the kalemia in almost all cases, from 97% to 100%, as reported by a consistent number of studies (37). In fact, in our series of 50 adrenalectomies who were followed up long term, all patients were and remained normokalemic throughout the follow-up serum evaluations. The most common symptom of primary aldosteronism, hypertension, had a percentage of cure after LA that was considerably lower than for hypokalemia. Over time many authors have collected data and parameters among Conn's patients. For instance, there are several experiences showing the pre-operative duration of hypertension, the poor response to spironolactone therapy before surgery, and the significant high blood pressure at discharge closely related to the risk persistence in spite of adrenalectomy (4, 38-41). Moreover, elderly patients seem to be less responsive to both pre-operative medication and operative procedure. As it is presumable that aged subjects suffer from long-standing hypertension, it is quite a syllogism to advocate as the main cause of difficult blood pressure control, the time progressing from transient to irreversible vascular wall damage (4). Sawka and coll. in 2001 presented a study in which they investigated potential factors associated with the resolution of hypertension after adrenalectomy. This study showed the cure of hypertension in patients with a lack of family history of hypertension and pre-operative treatment with fewer than two antihypertensive agents, in a series of 93 patients who had adrenalectomy and were followed up (42). Our results are in agreement with the aforementioned study pertaining to family history and pre-operative treatment. Moreover we found a higher rate of hypertension cure in younger patients and in the female sex. Indeed, in our series persistent hypertension requiring the maintenance of pre-operative therapy was observed after adrenalectomy in 5 cases who were hypertensive for more than 10 yr. To date, the estimated risk factors for post-operative persistent hypertension, such as age, sex, duration or pre-operative therapy, are reported with different influences (6, 42, 43). Finally there are studies of cost minimization analysis comparing the two treatment modalities of hypertension, the lifetime anti-hypertensive medication against the surgical procedure. The latter proved to be a cheaper form of treatment, evaluating both patients who completely ceased drug therapy and those who reduced it (44, 45).

CONCLUSIONS

LA is the procedure of choice for removing a large part of adrenal masses. Left LA by submesocolic route is an ulterior refinement toward minimally invasive surgery. Primary aldosteronism may be successfully treated by laparoscopy, with good results in term of kalemia and blood pressure normalization. Age of patients and duration of hypertension before surgery seem to be predictive factors of unsatisfactory response of blood pressure. Based on our data, it seems to be important to avoid long-term hypertension before surgery in order to improve the rate of blood pressure normalization post-operatively.

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