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Surgical outcomes of laparoscopic adrenalectomy for primary hyperaldosteronism: 20 years of experience in a single institution

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Purpose: Recently, posterior retroperitoneoscopic adrenalectomy (PRA) has been reported to have some advantages over laparoscopic transperitoneal adrenalectomy (LTA). The objectives of this study were to report our experience over 12 years with laparoscopic adrenalectomy for primary hyperaldosteronism (PHA) and to examine surgical outcomes of PRA compared with LTA in patients with PHA.

Methods: The medical records of 527 patients who underwent minimally invasive adrenalectomy, including LTA or PRA, from January 2006 until May 2017 were reviewed at Severance Hospital (Seoul, Korea). Clinicopathologic characteristics and surgical outcomes of 146 patients with PHA who underwent LTA (19 patients) or PRA (127 patients) were analyzed retrospectively by complete chart review.

Results: The overall rates of biochemical and clinical cure were 91.1% and 93.1%, respectively. The mean operation time of the PRA group was significantly shorter than that of the LTA group (72.3 ± 24.1 minutes *vs.* 115.7 ± 69.7 minutes, P = 0.015). The length of hospital stay in the PRA group was significantly shorter than in the LTA group (3.5 ± 1.3 days *vs.* 4.2 ± 1.6 days, P = 0.029), and the first meal after surgery came earlier in the PRA group (0.3 ± 0.5 days *vs.* 0.6 ± 0.5 days, P = 0.049). The number of pain-killers used was also significantly smaller in the PRA group (2.3 ± 2.1 *vs.* 4.3 ± 2.3, P < 0.001).

Conclusion: PRA offers an alternative or likely superior method for treatment of small adrenal diseases such as PHA, with improved surgical outcomes.

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Key Words: Hyperaldosteronism, Laparoscopy, Adrenalectomy

INTRODUCTION

Our understanding of primary hyperaldosteronism (PHA), also known as Conn syndrome, has advanced significantly since the first description by Conn approximately 60 years ago [1]. The definition of PHA is a group of disorders involving excessive production of aldosterone, autonomous from the renin-angiotensin system, and nonsuppression by sodium loading [2,3]. PHA is considered one of the most common causes of secondary hypertension [4]. Several studies have reported that PHA accounts for 1% to 10% of cases of hypertension [4-6].

PHA can be detected in either a bilateral or unilateral form. If patients are diagnosed with unilateral PHA, the treatment of choice is surgery [7,8]. Laparoscopic surgery is preferable to open surgery due to better safety, less morbidity, more rapid patient recovery, shorter operative times, and greater cosmesis [9,10]. The first laparoscopic transperitoneal adrenalectomy (LTA) was performed in 1992, and it has since become the

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standard treatment for benign adrenal tumors [11,12]. However, the transperitoneal approach has some disadvantages, such as risk of visceral damage, ileus after surgery due to bowel manipulation, and CO_2 retention, among others [13]. Posterior retroperitoneoscopic adrenalectomy (PRA) is now regarded as a better method for small (less than 7 cm) benign adrenal tumors [14]. A variety of studies have demonstrated that, compared with LTA, PRA has some advantages, including no manipulation of peritoneal organs, direct access to the adrenal gland, shorter operation times, less blood loss, less postoperative pain, and shorter length of hospital stay [15,16]. In contrast, the possibility of kidney injury, a smaller working space, and the difficulty of learning the technique are drawbacks to this procedure [17].

In this study, we analyzed cases of laparoscopic adrenalectomy over the last 12 years at our institution. The aims of this study were to describe our 12-year experience with laparoscopic adrenalectomy for PHA and compare surgical outcomes of PRA and LTA in patients with PHA.

METHODS

Patients

We retrospectively reviewed the medical records of 527 patients who underwent minimally invasive adrenalectomy, including LTA or PRA, from January 2006 until May 2017 at Severance Hospital (Seoul, Korea). We excluded patients with a non-functioning tumor (151 patients), Cushing disease (72 patients), pheochromocytoma (84 patients), paraganglioma (45 patients), or a metastatic adrenal mass (29 patients). Clinicopathologic characteristics and surgical outcomes of 146 patients who underwent LTA or PRA with PHA were analyzed by complete retrospective chart review. This study was approved by the local Institutional Review Board, which waived the requirement for informed consent due to the retrospective study design (approval number: 2017-1973-001).

Diagnosis of PHA

The appropriate timing to assess for PHA remains controversial. The Endocrine Society recommends tests for patients with the following problems [6,18]: (1) stage 2 of Joint National Commission, systolic/diastolic >160–179/100–109 mmHg; (2) stage 3 of Joint National Commission, systolic/diastolic >180/110 mmHg; (3) spontaneous hypokalemia or diuretic-induced hypokalemia in patients with hypertension; (4) adrenal incidentaloma in patients with hypertension; (5) drug-resistant hypertension; (6) a family history of early onset hypertension; (7) cerebrovascular event at less than 40 years old; and (8) first-degree relatives with PHA. The most common screening test for PHA is the serum aldosterone and plasma renin activity ratio (ARR), which has higher sensitivity and specificity than either aldosterone or plasma renin activity alone [6,19]. Following an increased ARR over 30 in our institution, the second step for diagnosis of PHA is a confirmatory test, such as oral salt loading, salt infusion test (SIT), fludrocortisone stimulation test, and captopril or losartan challenge test [6]. Of these, our hospital mainly uses SIT. All patients who were screened and underwent confirmatory tests temporarily discontinued their antihypertensive drugs for at least 2 weeks, including diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, and β-blockers. Mineralocorticoid receptor antagonists were stopped for at least four weeks.

Lateralization with adrenal venous sampling

CT is significantly useful for identifying adrenal tumors. However, even though CT has better sensitivity and specificity for finding adrenal tumors than magnetic resonance imaging, the detection rate of CT for small tumors (less than 1 cm in diameter) is only 50% [6]. Lateralization with adrenal venous sampling (AVS) is important for distinguishing unilateral and bilateral PHA and for determining the treatment of choice [20]. The AVS procedure was described in a previous paper [21]. For C-arm CT-assisted AVS, the right femoral vein was accessed under ultrasonographic guidance. After catheterization and venography of the right adrenal vein, 3-dimensional multiplanar reconstruction images by C-arm CT were used to verify proper catheter position. Left AVS was performed without a C-arm CT scan. Blood samples were drawn in the order of right adrenal vein, left adrenal vein, and infrarenal inferior vena cava. The success rate of C-arm CT-assisted AVS is approximately 95% in our institution [22]. The sensitivity and specificity for detection of lateralization are 95% and 100%, respectively [23]. The analysis of AVS lateralization was as follows: (1) if lateralization index (LI) was more than 4, unilateral PHA, (2) if LI was less than 3, bilateral PHA, (3) if LI was over 3 and less than 4, grey zone [24].

Surgical procedure

Among patients with PHA, adrenalectomy was performed only for unilateral disease identified by diagnostic tests. The surgical procedures for PRA and LTA have been previously described [14,25,26]. For LTA, patients were placed into the lateral decubitus position. Three trocars were usually used for left-side adrenalectomy, and 4 trocars were used for right-side adrenalectomy for liver retraction (Fig. 1) [25,26]. For PRA, patients were prepared in the prone position lying on a soft bar below both the anterior and superior iliac spine. The surgical table was tilted with the head downward about 10°. A 1.5-cm skin incision was made just below the lowest tip of the 12th rib. A 1.0-cm port site was made about 4 cm medial from the first skin incision for the camera, and the third 0.5-cm trocar was inserted about 4 cm lateral from the first skin incision along

the lowest margin of the 11th rib (Fig. 2). CO_2 gas at a pressure of 18 to 20 mmHg was injected to maintain the work space. A 10 mm or 5 mm/30° camera was placed into the medial trocar. To expose the adrenal gland, Gerota's fascia and perinephric fat tissue were delicately dissected. The adrenal vein was ligated with 5-mm clips, and the specimen was removed from the retroperitoneal space using an endoscopic retrieval bag [14,25].

Statistical analysis

All statistical analyses were carried out using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). We reported continuous variables as the mean value with standard deviation and categorical variables as numbers with percentages. Comparisons between preoperative and postoperative surgical outcomes were performed using the paired t-test. Chi-square test or Fisher exact test was performed to compare categorical variables between LTA and PRA. A statistically significant difference was defined as $P < 0.05$.

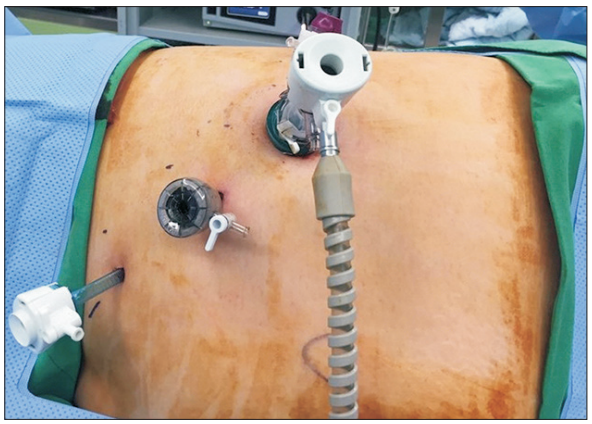

Fig. 1. Patient and trocar position of laparoscopic transperitoneal adrenalectomy.

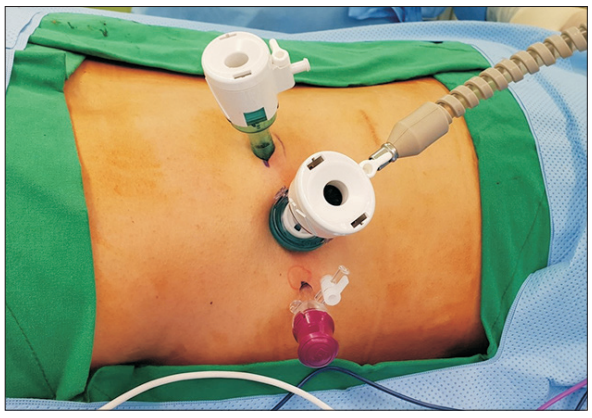

Fig. 2. Patient and trocar position of posterior retroperitoneoscopic adrenalectomy.

RESULTS

Baseline clinicopathologic characteristics

During the study period, a total of 146 patients were identified as undergoing LTA or PRA for PHA. Table 1 presents baseline clinicopathologic characteristics obtained from the complete chart review. The mean age was 48.3 years (range, 22–81 years). Eighty-five patients (58.2%) were female, and the mean body mass index (BMI) was 24.9 kg/m^2 (range, 18.1–41.0 kg/m^2). A total of 94 patients (64.4%) underwent AVS examination; among them, 71 patients (75.5%) were diagnosed with successful lateralization, and the LI of 23 patients (24.4%) was less than 4. The mean tumor size was 2.0 cm (range, 0.5–11.7 cm). The majority of patients (134 [91.8%]) underwent laparoscopic surgery, and the rest (12 [8.2%]) were operated on using a robotic system. PRA was performed in 127 patients (87.0%), and the remaining 19 patients (13.0%) underwent LTA. There were 56 patients (38.4%) who underwent right-side surgery, while 90 patients (61.6%) received a left-side operation.

Perioperative outcomes

Surgical and clinical outcomes are summarized in Tables 2 and 3. The mean operation time was 78.0 minutes (range, 41–389 minutes), and there were 3 complications, all port-site

Table 1. Baseline clinicopathologic characteristics of the study patients (n = 146)

Characteristic	Value
Age (yr)	48.3 ± 11.6 (22–81)
Sex, male:female (ratio)	61:85 (1:1.4)
Body mass index (kg/m^2)	24.9 ± 4.1 (18.1–41.0)
AVS	
Yes	94 (64.4)
No	52 (35.6)
AVS lateralization (ratio)	
≥4	71/94 (75.5)
3≤, <4	7/94 (7.4)
<3	16/94 (17.0)
Tumor size (cm)	2.0 ± 1.4 (0.5–11.7)
Operation method	
Laparoscopic	134 (91.8)
Robotic	12 (8.2)
Approach	
PRA	127 (87.0)
LTA	19 (13.0)
Operation side	
Right	56 (38.4)
Left	90 (61.6)

Values are presented as mean ± standard deviation (range) or number (%).
AVS, adrenal venous sampling; PRA, posterior retroperitoneoscopic adrenalectomy; LTA, lateral transperitoneal adrenalectomy.

seromas. The mean length of hospital stay was 3.6 days (range, 2–9 days). The majority of patients (100 [68.5%]) started to eat on the day of surgery, and 41 patients (28.1%) started the day after. The mean number of pain-killers (tridol 50 mg, keromin 30 mg, or pethidine 25 mg) used after surgery was 2.5 injections (range, 0–10 injections). The mean preoperative and postoperative serum ARR were 282.7 (range, 1.12–1,674.4) and 14.2 ng/dL per ng/mL/hr (range, 0.02–100.7 ng/dL per ng/mL/hr), respectively. The number of biochemically cured (defined as ARR < 30 ng/dL per ng/mL/hr and normokalemia without any diuretics in the 6 months after surgery) patients was 133 (91.1%). The preoperative number of antihypertensive drugs used was 2.5 (range, 0–6), and the number used after surgery was 0.9 (0–4). The number of clinically cured patients after surgery was 136 (93.1%); 63 (43.1%) were completely cured (defined as blood pressure less than 140/90 mmHg without the aid of antihypertensive drugs in the 6 months after surgery) and 73 (50.0%) were improved (defined as a reduction of at least one antihypertensive drug in the 6 months after surgery). Ten patients (6.9%) were unable to reduce the number of anti-hypertensive drugs after surgery.

As shown in Table 4, ARR and the number of antihypertensive drugs used were compared between preoperative and postoperative periods. The ARR was significantly lower after surgery (282.7 ± 344.4 ng/dL per ng/mL/hr *vs.* 14.2 ± 18.1 ng/dL per ng/mL/hr, P < 0.001), and the number of antihypertensive drugs used improved significantly after surgery (2.5 ± 1.2 *vs.* 0.9 ± 0.9, P < 0.001).

Table 2. Surgical outcomes of study patients who underwent adrenalectomy (n = 146)

Variable	Value
Operation time (min)	78.0 ± 36.4 (41–389)
Complication	3 (2.1)
Length of hospital stay (day)	3.6 ± 1.4 (2–9)
First diet after operation	
POD #0	100 (68.5)
POD #1	41 (28.1)
POD #2	5 (3.4)
No. of pain-killer used	2.5 ± 2.3 (0–10)

Values are presented as mean ± standard deviation (range) or number (%).
POD, postoperative day.

Table 3. Clinical outcomes for primary hyperaldosteronism after operation

Variable	Value
Preoperative ARR (ng/dL per ng/mL/hr)	282.7 ± 344.4 (1.12–1,674.4)
Postoperative ARR (ng/dL per ng/mL/hr)	14.2 ± 18.1 (0.02–100.7)
No. of biochemically cured	133 (91.1)
Preoperative No. of antihypertensive drugs used	2.5 ± 1.2 (0–6)
Postoperative No. of antihypertensive drugs used	0.9 ± 0.9 (0–4)
No. of clinically cured	136 (93.1)
Completely cured	63 (43.1)
Improved	73 (50.0)
Sustained	10 (6.9)

Values are presented as mean ± standard deviation (range) or number (%).
ARR, serum aldosterone and plasma renin activity ratio.

Comparison of surgical outcomes between PRA and LTA groups

Table 5 compares baseline clinicopathologic characteristics and perioperative outcomes between the PRA and LTA groups. There was no statistically significant difference in age, sex, BMI, tumor size, preoperative ARR, postoperative ARR, or preoperative number of antihypertensive drugs used between the 2 groups.

Left-side surgery was predominant in the LTA group (P = 0.001). The mean operation time for the PRA group was significantly shorter than that of the LTA group (72.3 ± 24.1 minutes *vs.* 115.7 ± 69.7 minutes, P = 0.015). The length of hospital stay in the PRA group was significantly shorter than in the LTA group (3.5 ± 1.3 days *vs.* 4.2 ± 1.6 days, P =0.029), and the time to first meal after surgery was also shorter in the PRA group (0.3 ± 0.5 days *vs.* 0.6 ± 0.5 days, P = 0.049). The number of pain-killers used was significantly fewer in the PRA group (2.3 ± 2.1 *vs.* 4.3 ± 2.3, P < 0.001). However, the postoperative number of antihypertensive drugs used in the LTA group was significantly fewer than in the PRA group (0.3 ± 0.5 *vs.* 0.9 ± 0.9, P = 0.011).

DISCUSSION

PHA has likely been underestimated because of the difficulty of diagnosis without suspicion. ARR is widely used as a screening test for PHA in hypertensive patients. AVS is the gold standard for differentiating between unilateral and

Table 4. Comparison of perioperative ARR and number of antihypertensive drugs used

Variable	Preoperative	Postoperative	P-value
ARR (ng/dL per ng/mL/hr)	282.7 ± 344.4 (1.1–1,674.4)	14.2 ± 18.1 (0.02–100.7)	<0.001
No. of antihypertensives used	2.5 ± 1.2 (0–6)	0.9 ± 0.9 (0–4)	<0.001

Values are presented as mean ± standard deviation (range) or number (%).
ARR, serum aldosterone and plasma renin activity ratio.

Table 5. Comparison of baseline characteristics and perioperative outcomes between PRA and LTA groups

Variable	PRA (n = 127)	LTA (n = 19)	P-value
Age (yr)	48.7 ± 11.8	45.8 ± 10.4	0.307
Sex, male:female (ratio)	53:74 (1:1.4)	8:11 (1:1.4)	0.975
Body mass index (kg/m^2)	25.1 ± 4.1	23.9 ± 4.5	0.252
Operation side			0.001
Right	55 (43.3)	1 (5.2)	
Left	72 (56.7)	18 (94.7)	
Operation time (min)	72.3 ± 24.1	115.7 ± 69.7	0.015
Tumor size (cm)	1.9 ± 1.1	2.5 ± 2.6	0.310
Length of hospital stay (day)	3.5 ± 1.3	4.2 ± 1.6	0.029
First diet after operation	0.3 ± 0.5	0.6 ± 0.5	0.049
POD #0	92 (72.4)	8 (42.1)	
POD #1	30 (23.6)	11 (57.9)	
POD #2	5 (3.9)	0 (0)	
No. of pain-killer used	2.3 ± 2.1	4.3 ± 2.4	<0.001
Preoperative ARR (ng/dL per ng/mL/hr)	284.3 ± 336.6	296.2 ± 410.8	0.895
Postoperative ARR (ng/dL per ng/mL/hr)	14.7 ± 18.5	11.3 ± 15.0	0.475
Preoperative No. of antihypertensive drugs used	2.4 ± 1.1	2.5 ± 1.2	0.699
Postoperative No. of antihypertensive drugs used	0.9 ± 0.9	0.3 ± 0.5	0.011

Values are presented as mean ± standard deviation or number (%).
PRA, posterior retroperitoneoscopic adrenalectomy; LTA, lateral transperitoneal adrenalectomy; POD, postoperative day; ARR, serum aldosterone and plasma renin.

bilateral disease. In our institution, C-arm CT-assisted AVS has been performed for lateralization since 2011 [22]. In this study, 92 patients (73.6%) who underwent adrenalectomy after 2011 had an AVS examination. In contrast, only 2 of 21 patients (9.5%) who underwent adrenalectomy before 2011 had an AVS examination. Even though 23 of 94 patients (24.4%) were diagnosed with an LI less than 4, they still underwent adrenalectomy. PHA was suspected because the suppression index (defined as the measure of inhibition of aldosterone secretion in the adrenal gland contralateral to an ipsilateral lesion [24]), which was calculated as the ratio of the cortisol-corrected aldosterone ratio (AC) of the nondominant adrenal gland to the peripheral AC, was less than 1 or clinically unilateral [27].

Cure rate in patients with PHA after adrenalectomy has been reported in the range from 35% to 60% in previous studies [2,28]. Our cure rate was 43.1% and improved rate was 50%. However, the remaining 10 patients (6.9%) maintained their anti-hypertensive drug use even after surgery, possibly due to a longer hypertension morbidity period or bilateral PHA.

The treatment of choice for unilateral PHA is surgery, minimally invasive adrenalectomy in particular, which is identified as safe; surprisingly, there were only 3 complications of port-site seromas in this study. There are 2 minimally invasive approach methods: LTA and PRA. LTA is the most widely performed method and has some advantages in terms of large working space and a familiar anatomical view. On the other hand, even though PRA is only recommended for small adrenal tumors less than 7 cm, it has many advantages, such as direct exposure of the adrenal gland, no manipulation of adjacent organs, and a relatively shorter operation time.

To compare surgical outcomes between LTA and PRA, we used several perioperative parameters, including operation time, the number of pain-killers used after surgery, length of hospital stay, and time to first meal after surgery. Previous studies report that the mean operation time is shorter for PRA than for LTA [29], and our findings agreed. The requirement for pain-killers was also significantly lower in the PRA group, possibly because of the shorter operation time, small surgical dissection, and need for only three trocars regardless of the side of the operation. The same reasons may have also influenced the length of hospital stay and time to first meal after surgery. However, the only three minor complications occurred in the PRA group; all were port-site seromas that were taken care of by a simple dressing in outpatient care.

We note that there are some limitations to the present study such as its retrospective case-control design and restriction to a single tertiary institution. The LTA group had relatively fewer patients than the PRA group because PRA was predominantly performed for adrenal diseases after 2009 in our institution. In accordance with the patients' hypertension morbidity period, the degree of reduction in postoperative number of antihypertensive drugs used also varied considerably and was not described in a majority of patients' medical records. Furthermore, we excluded perioperative blood pressure and potassium levels, because most patients (85.6%) had

taken spironolactone and potassium chloride medication since diagnosis of PHA and underwent adrenalectomy in a normalizing condition of blood pressure and potassium status. Finally, we simply compared the number of pain-killers used between the 2 groups without consideration of dose or type of pain-killer, and pain scores such as visual analog scale were not evaluated after surgery.

In conclusion, PHA is a complex disease from diagnosis to treatment. LTA is still the most widely used surgical approach for unilateral adrenal diseases. In our study, we described the range of disease cure rate through laparoscopic adrenalectomy, with excellent surgical outcomes for the management of PHA using PRA. PRA offers an alternative or likely superior method for treating small adrenal diseases such as PHA, with improved surgical outcomes.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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