

## OUTCOMES AFTER LAPAROSCOPIC ADRENALECTOMY FOR UNILATERAL PRIMARY ALDOSTERONISM

WALTER S. NARDI<sup>1</sup>, MARIANA TOFFOLO<sup>1</sup>, MARICEL RECALDE<sup>2</sup>, MELINA SABAN<sup>2</sup>, MIGUEL SCHIAVONE<sup>3</sup>, SERGIO D. QUILDRIAN<sup>1</sup>

<sup>1</sup>Unidad de Tumores Retroperitoneales, Pélvicos y Adrenales, Servicio de Cirugía General,

<sup>2</sup>Servicio de Endocrinología, <sup>3</sup>Servicio de Cardiología, Hospital Británico de Buenos Aires, Buenos Aires, Argentina

**Abstract** Unilateral primary aldosteronism (PA) is the most common surgically correctable cause of hypertension. Determination of success after laparoscopic adrenalectomy (LA) is limited by the lack of standardized criteria. We sought to evaluate the surgical recurrence and functional outcomes of LA in patients with Conn's syndrome applying the primary aldosteronism surgical outcome (PASO) Criteria. Descriptive observational analysis of patients treated with LA due to confirmed unilateral Conn's syndrome between May 2007 and August 2020: Twenty patients were included in the cohort; 16 patients had TLA and other four PLA [58% male, median age 47 (IQR: 44-59.5) years and median follow-up of 64 (IQR: 2-156) ] months. Median tumor size was 1.2 (0.8-1.8) cm. No conversions to open surgery were recorded and the overall morbidity of the series was 1/20. No surgical or biochemical recurrence was observed. Five patients were excluded from the analysis of functional results due to lack of follow-up. According to the PASO criteria, complete, partial, and no success were observed in 8/15, 6/15, and 1/15, respectively. The surgical treatment of the disease is supported by the literature, and we were able to reproduce the results of other series. The use of standardized and reproducible criteria to assess its functional results would be essential for a more complete and integrated evaluation of adrenal surgery.

**Key words:** primary aldosteronism, laparoscopic adrenalectomy, standardized criteria, Conn's syndrome

### **Resumen** *Resultados luego de adrenalectomía laparoscópica en hiperaldosteronismo primario unilateral*

El hiperaldosteronismo primario es la causa más frecuente de hipertensión secundaria pasible de tratamiento quirúrgico. La determinación del éxito de la adrenalectomía laparoscópica (AL), actualmente, está limitada por la falta de criterios estandarizados. Buscamos evaluar la tasa de recurrencia quirúrgica y los resultados funcionales de la AL en pacientes con Síndrome de Conn aplicando los criterios PASO (*primary aldosteronism surgical outcome*). Análisis descriptivo y observacional de pacientes tratados con AL en contexto de síndrome de Conn unilateral confirmado, entre Mayo-2007 y Agosto-2020. Se incluyeron 20 pacientes en el estudio; 16 pacientes tratados mediante AL total y 4 con AL parcial (55% hombres, edad mediana de 47 (IQR: 44-59.5) años y mediana de seguimiento 64 (IQR: 2-156) meses. La mediana de tamaño tumoral fue de 1.2 (0.8-1.8) cm. No se registraron conversiones a cirugía abierta y la morbilidad global de la serie: 1/20. No se observó recurrencia quirúrgica o bioquímica. Se excluyeron 5 pacientes en el análisis de resultados funcionales por falta de seguimiento. Según los criterios PASO, se observó un éxito completo, parcial y ausente en 8/15, 6/15 y 1/15, respectivamente. El tratamiento quirúrgico de la enfermedad es avalado por la literatura y pudimos reproducir los resultados de otras series. El uso estandarizado y reproducible de criterios para valorar sus resultados funcionales sería fundamental para una evaluación más completa e integrada de la cirugía suprarrenal.

**Palabras clave:** hiperaldosteronismo primario, adrenalectomía laparoscópica, estandarización de criterios

### KEY POINTS

- **Current knowledge:** Surgical treatment for unilateral primary hiperaldosteronism continues to be supported by the literature. Besides the technique chosen (total or partial laparoscopic adrenalectomy), the reported cure rates vary. An international consensus established clear criteria to assess clinical and biochemical success (PASO Criteria)
- **Article contribution:** According to the PASO guidelines, we had an overall complete and partial clinical success of 53% and 40%, respectively. Common use of standardized and reproducible functional outcomes criteria is critical for a more comprehensive evaluation of adrenal surgery.

Unilateral primary aldosteronism (PA) is the most common surgically correctable cause of hypertension and most common cause of secondary hypertension. Its importance relies in the resolution of excess risk of cardiovascular and cerebrovascular morbidity and mortality after surgical treatment<sup>1,2</sup>.

Since the first total laparoscopic adrenalectomy (TLA) was described by Gagner in 1992<sup>1</sup>, this approach has become the preferred and standard operation for patients with adrenal masses. Moreover, in the last 2 decades the number of adrenalectomies performed has increased<sup>2</sup>. While most of adrenal tumors are small and nonfunctional, up to 15% are biochemically active<sup>3</sup>. Many patients with small benign adrenal tumors undergo total adrenalectomy. In many cases, a normal contralateral adrenal gland may be dysfunctional due to a functional mass in the opposite gland. A major experience with laparoscopic technique has lead in recent years to evaluate the utility of partial laparoscopic adrenalectomy (PLA) in selected patients. The objective is to avoid the side effects of a potential adrenal insufficiency or lifelong steroid dependency by preserving adrenal cortex as much as possible<sup>4-7</sup>.

We sought to evaluate the surgical recurrence and functional outcomes of laparoscopic adrenalectomy (TLA and PLA) in patients affected by Conn's Syndrome with a solitary adrenal mass according to the Primary Aldosteronism Surgical Outcome (PASO) criteria<sup>8</sup>.

### Materials and methods

We performed a descriptive observational analysis of patients with confirmed Conn's syndrome treated at our Institution with TLA or PLA from May 2007 through August 2020. Primary aldosteronism was diagnosed according to the US Endocrine Society guidelines<sup>9</sup>. Biochemical evidence of PA was defined by increased serum aldosterone level ( $\geq 310$  pg/mL), sup-

pressed plasma renin activity ( $< 1$  ng/dL/h) or hypokalemia ( $< 3.6$  mmol/L). Also, the diagnosis of PA was confirmed by an aldosterone-to-renin ratio (ARR)  $> 200$ . Surgery was performed in all patients  $> 18$  years with a single, unilateral adrenal mass diagnosed on computer tomography or magnetic resonance imaging. Hence, our aim was to describe perioperative outcomes of patients with minimally invasive adrenalectomy for unilateral localized PA. Partial resection was performed if the surgeon could clearly localize the adrenal adenoma and differentiate it from normal adrenal tissue. If not, total adrenal resection was performed. Patients with bilateral adrenal masses, history of oncological disease or missing perioperative surgical data were all excluded from the analysis. Demographic, perioperative data, clinical-biochemical outcomes and follow-up data were evaluated on individual medical records. Complications within 30 days of surgery were registered according to the Clavien-Dindo classification<sup>10,11</sup>. Functional results (clinical and biochemical) were informed and classified according to the PASO criteria<sup>8</sup>. A comprehensive evaluation was performed during postoperative follow-up at 3, 6 and 12 months after the surgery by the 3 Departments involved (Endocrinology, Cardiology and Surgery). Biochemical success was defined as normalization of ARR or potassium levels at 6 months or greater postoperatively. Complete clinical success was defined as normal systolic blood pressure (SBP) according to the European Society of Hypertension guidelines (e.g.  $< 140$  mm Hg for the outpatient setting)<sup>12</sup> without the aid of antihypertensive medication at  $\geq 6$  months after adrenalectomy. Partial clinical success was considered in cases of same SBP with less amount of antihypertensive medication or reduction of SBP with either the same or less amount of antihypertensive medication or switch to a lower class of medication<sup>12</sup>. Finally, patients were categorized as having absent clinical success if unchanged or increased SBP with the same or even increased antihypertensive medication.

According to the distribution of the variables we used median (IQR: 25-75%) in continuous variables. The Mann Whitney test was used to compare the groups. Categorical variables were registered as absolute numbers.

Ethical approval was waived by local Ethics Committee of British Hospital of Buenos Aires in view of retrospective nature of the study, and all the procedures being performed were part of the routine care. Due to the retrospective nature of this study, the Ethics Committee waived the requirement for written informed consent. Nevertheless, all patients signed the surgical consent form.

### Results

A total of 20 adrenalectomies due to Conn's syndrome were performed over the study period; 11 patients were male and the median age was 47 (IQR: 44-59.5) years. Regarding the site of the adrenal mass: 12 cases were right-sided and 8 left-sided. The median tumor size of the whole cohort was 1.2 (0.8-1.8) cm. At final pathology assessment: 19 patients had encapsulated adenomas and 1 patient showed diffuse adrenal hyperplasia with an adenoma. None of the total adrenalectomy specimens had more than one nodule in the pathological examination. Demographic and pre-operative characteristics of the entire cohort are summarized in Table 1.

We performed a laparoscopic unilateral adrenalectomy on all patients via the anterior approach (16 TLA and 4 PLA). Median operative time was 120 (IQR: 105-135) minutes. There were no intra-operative events and all surgical procedures were performed without conversion to open surgery. No deaths were observed in the perioperative period or during the follow-up. The overall complication rate was 1/20 corresponding to one grade-II complication in a patient who presented atrial fibrillation and needed a pharmacological cardioversion. Table 2 shows the perioperative outcomes.

The median follow-up was 64 (IQR: 2-156) months. We decided to exclude 5 patients from the functional outcome analysis due to loss of the last 2 or more endocrinologic controls, leaving a total of 15 patients in this section (11 patients with TLA and 4 with PLA). Functional outcomes are shown in Table 3. A complete, partial and absent clinical success was observed in 8, 6 and 1, respectively. No

recurrence was observed. All patients with pre-surgery hypokalemia had a complete biochemical success through correction of potassium serum levels and normalization of ARR ratio. At time of last follow-up, none of the patients required potassium supplements post-operatively and all are free of exogenous steroid replacement therapy. Of the 15 patients analyzed, 13 had pre-operative antihypertensive drugs; 6 belonged to the complete and 6 to the partial clinical success groups with a median number of 1 and 2.5 agents taken, respectively. Of note: the patient in the absent clinical success group had history of duration of hypertension > 16 years and used 4 antihypertensive agents. In fact, patients who had a partial and absent clinical success taken together as a subgroup (n = 7) took more number of preoperative antihypertensive drugs when compared with patients who achieved complete clinical response (p = 0.04). There were no other differences among the groups (Table 4).

TABLE 1.– Demographic and pre-operative data

Characteristic	n
Sex (male/female)	11/9
Age, median (y)*	47 (44-59)
ASA score, (n)	
1-2	16
3-4	4
Side, (n)	
Right	12
Left	8
Adrenal mass size (cm)*	1.2 (0.8-1.8)
Pre-operative symptoms	
Hypertension	2
Hypokalemia (< 3.6 mmol/l)	2
Both	6

ASA: American Society of Anesthesiologists

\*Median (interquartile range)

TABLE 2.– Operative data

Variable	n
Type of adrenalectomy	
Total	16
Partial	4
Operative time (min)*	120 (105-135)
Drainage	2
Conversion to open approach	0
LOS (d)*	1.5 (1-4)
Clavien grade, n	
I-II	0
III-IV	1
V	0

LOS: Length of stay

\*Median (interquartile range)

TABLE 3.– Outcomes according to primary aldosteronism surgical outcome (PASO) criteria in 15 patients

Variable	n
Complete clinical success	8
Partial clinical success	6
Decreased dosage medication	3
Switch to a lower class of medication	3
Absent clinical success	
Unchanged antihypertensive medication	1
Hypokalemia (< 3.6 mmol/L)	0

TABLE 4.– Patient's clinical characteristics (functional outcome analysis cohort)

Variable	Total n = 15	Complete clinical success n = 8	Partial + absent clinical success n = 7	p value
Age (y)*	47 (44-59)	48.5 (39.25-61)	45 (39-55)	0.51
Male sex	8	3	5	0.31
Duration of HTN (y)*	2 (1-4)	2 (1-4)	2 (0-3)	0.46
Preoperative # of antihypertensive drugs*	2 (1-3)	1 (0.25-2)	3 (1-3)	0.04
BMI (kg/m <sup>2</sup> ) *	27.8 (24.2-30.7)	28 (23.4-32.1)	29.9 (24.3-31.2)	0.68
History of cardiovascular events	2	1	1	0.99
Diabetes	3	1	2	0.56
Current smoker	3	1	2	0.56
ASA Score				
1	1	0	1	0.46
2	11	6	5	0.99
3	3	2	1	0.99
4	0	0	0	0.99
Preoperative serum potassium (mEq/L)*	3.5 (3.1-4.3)	3.6 (3.2-4.2)	3.4 (3-4.7)	0.70
Preoperative serum aldosterone (pg/mL)*	335 (318-423)	336 (321-399.5)	335 (312-449)	0.70
Surgical procedure performed				
Total adrenalectomy	11	6	5	0.99
Partial adrenalectomy	4	2	2	0.99
Tumor size, cm*	1 (0.7-1.5)	1.35 (0.92-2.1)	0.8 (0.7-1.2)	0.08
Tumor laterality				
Left	7	3	4	0.62
Right	8	5	3	0.62

HTN: hypertension; BMI: body mass index; ASA: American Society of Anesthesiologists

\*Median (interquartile range)

## Discussion

Nowadays, TLA is still considered the gold standard approach for the treatment of PA but, PLA has demonstrated being a safe and feasible alternative in several studies<sup>13, 14</sup>. However, besides the surgical technique chosen, the absence of standardized criteria for evaluation and reporting of functional outcomes was still a need. In literature, the reported cure rates vary. In 2017, an international consensus established clear criteria to assess complete, partial, absent clinical and biochemical success<sup>6</sup>. Recently, some authors

have chosen to use these criteria. We decided to start applying these consensus definitions in order to standardize our results. We therefore present our preliminary surgical and functional results of laparoscopic adrenalectomy for the treatment of PA. To the best of our knowledge, is the first national study to evaluate the functional results of laparoscopic adrenalectomy using the PASO criteria.

Numerous large case series have demonstrated that minimally invasive surgical treatment of PA is safe, has low morbidity and short hospital stay<sup>15, 16</sup>. We had an overall morbidity rate of 5.2% and a median hospital length of

stay of 1.5 days. Nevertheless, while postoperative results have been shown to be positive, functional benefits must be critically evaluated. Historically, clinical success of surgery for unilateral PA varied significantly in the literature owing to a lack of consensus to define what was considered success. Applying the PASO criteria proposed by Williams et al.<sup>8</sup> we report a complete and partial clinical success of 8 and 6 patients respectively in our preliminary cohort. Thus, one patient had no clinical benefit from the surgery. In their published study in 2017 they report a complete and partial clinical success of 37% and 47% respectively out of 705 patients<sup>8</sup>. In addition, other authors have previously used the PASO criteria. Sellgreen et al.<sup>18</sup> reported in 2019, 34% of complete and 60% partial clinical success after surgery (most using a minimally invasive approach). Billman et al.<sup>19</sup> in 2020 reported complete and partial success rates of 40.6% and 52.6% using the same criteria. Interestingly, they did not find significant differences between TLA and PLA in terms of success, both complete and partial. Because of the small sample size, comparing both groups was not an aim in our study. Other authors, such as Anceschi et al.<sup>20</sup>, had different results. They reviewed 90 patients, including 29 in the PLA group and 61 in the TLA group. In their study, the median tumor size was significantly higher in TLA group. They demonstrated that PLA group had better complete clinical success than TLA group, partial clinical success was significantly higher in TLA group and absent clinical success rate was similar in both groups.

Is interesting to note that adrenal sparing surgery has gained popularity over the last years and is being done more often worldwide<sup>21</sup>. Conn's Syndrome is the most common cause and a possible reason that has made this alternative possible, is that lesions are often small, solitary and located in the margin of the gland. We think the location is an important criterion to choose a cortical-sparing approach. Moreover, various series have demonstrated the safety and feasibility of the partial adrenalectomy laparoscopic approach, not even having differences with the standard technique<sup>20-23</sup>. However, different histological findings in patients with unilateral disease (i.e adrenal hyperplasia, combined adenoma and hyperplasia or multiple adenomas) may be present in up to 27% of the patients<sup>23, 24</sup>, suggesting an increased risk of failure after surgical treatment<sup>25</sup>. We performed 16 TLA and found only one patient having a combined adenoma with hyperplasia. Nagaraja et al.<sup>26</sup> report in a meta-analysis a great efficacy of partial adrenalectomy for the treatment of Conn's Syndrome with a recurrence rate of 2% that could not definitively be linked to the surgical technique and 97% of patients free of corticosteroid treatment. In our study, no recurrence after partial resection was observed during follow-up (median 26 months). All four PLA shown to be adrenal adenomas in the pathologic examination.

Hypertension is the rule in patients diagnosed with PA. In addition, aldosterone excess has deleterious effects on the cardiovascular systems that are independent of its effects on blood pressure<sup>27-29</sup>. It is therefore not sufficient to control only the hypertension in PA. Recent results published in the literature highlight the importance of surgery in PA. If possible, unilateral adrenalectomy in the setting of PA has been shown to reverse the cardiovascular morbidity more effectively than medical treatment<sup>1, 2, 30-32</sup>. Hence - as Billman et al.<sup>19</sup> hypothesized- even in the absence of a complete clinical success, surgery may benefit patients by decreasing systolic blood pressure or reducing the number of antihypertensive drugs taken by the patient with a subsequent decrease in morbidity<sup>33-35</sup>.

Evidence shows that there are several factors associated with hypertension resolution including having one or no first-degree relative with hypertension or preoperative use of 2 or less antihypertensive drugs<sup>36</sup>. Other factor is duration of hypertension < 5 years<sup>36-37</sup>. In our cohort 3/6 patients with partial clinical success had > 2 pre-operative antihypertensive drugs as well as the one patient with absent clinical success who also had duration of hypertension > 5 years as previously commented. When comparing the complete vs. partial/absent clinical success groups we were not able to find a statistical significance regarding this feature probably due to the size of the cohort. Nevertheless, in patients who took > 2 antihypertensive drugs the difference reached a statistical difference.

We are aware that the small number and retrospective nature of the cohort is a limitation of our study. Also, assessment of SBP could be affected by comorbidities, type of measurement and antihypertensive drugs used. Finally, the lack of evaluation of biochemical parameters instead of serum potassium levels remains an aspect to further investigate. Nonetheless, we strongly emphasize the multidisciplinary assessment of patients and show the first national study using standardized outcomes criteria.

In our series, laparoscopic adrenalectomy for Conn's disease was a secure procedure without mortality and low rate of postoperative complications. According to the PASO guidelines, we had an overall complete and partial clinical success of 53% and 40%, respectively. PLA was used in selected patients and seems to be an option to TLA but the low number of procedures precludes making a clear recommendation. The surgical treatment of unilateral disease is supported by the literature and we were able to reproduce the results of other series. We believe that the common use of standardized and reproducible functional outcomes criteria is critical for a more comprehensive evaluation of adrenal surgery.

**Conflict of interest:** None to declare

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