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Clinical Research Article

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Tolerability and Efficacy of Long-Term Medical Therapy in Primary Aldosteronism

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Abbreviations: APR, aldosterone-potassium ratio; AVS, adrenal vein sampling; CT, computed tomography; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonists; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PASO, Primary Aldosteronism Surgery Outcome; PRA, plasma renin activity; QOL, quality of life; SLT, saline infusion test.

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Abstract

Introduction: Patients with primary aldosteronism (PA) have increased cardiovascular risk, and there are concerns about the efficacy of medical therapy.
Objective: We aimed to assess long-term tolerability and efficacy of medical therapy in PA patients.
Methods: We conducted a retrospective study on 201 PA patients treated with medical therapy (spironolactone, eplerenone, or amiloride) from 2000 to 2020 at 2 tertiary centers. Clinical and biochemical control and side effects were assessed.
Results: Among 155 patients on long-term medications, 57.4% achieved blood pressure (BP) <140/90 mmHg, 90.1% achieved normokalemia (48.0% potassium ≥4.3 mmol/L), and 63.2% achieved renin >1 ng/mL/h. Concordance of biochemical control using potassium and renin levels was 49.1%. Side effects were experienced by 52.3% of patients, with 10.3% switching, 22.6% decreasing dose, and 11.0% stopping medications. Risk factors for side effects were spironolactone use, dose ≥ 50 mg, treatment duration ≥1 year, male

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gender, and unilateral PA. Patients with unilateral PA used higher spironolactone doses vs bilateral (57 vs 50 mg, $P < 0.001$) and had more side effects (63.2% vs 41.8%, $P = 0.008$). Forty-six unilateral PA patients who underwent surgery after initial medical therapy experienced improved BP (systolic from 141 to 135 mmHg, $P = 0.045$; diastolic from 85 to 79 mmHg, $P = 0.002$).

Conclusion: Dose-dependent side effects limit efficacy of medical therapy in PA. Future prospective studies should assess the best monitoring strategy for biochemical control during long-term medical therapy. For unilateral PA, surgery remains preferable, yielding better control with less long-term side effects.

Key Words: adrenal vein sampling, adrenalectomy, endocrine hypertension, subtyping, mineralocorticoid receptor antagonists

From 5% to 20% of all patients with hypertension have an underlying and treatable condition of primary aldosteronism (PA) [1]. Compared to patients with essential hypertension with similar blood pressure control, patients with PA are at greater risk of cardiovascular events, stroke [2], and renal failure [3], and have poorer quality of life (QOL) [4]. This has been attributed to the direct deleterious effects of aldosterone excess [5]. Hence, it is recommended that PA is specifically treated with either mineralocorticoid receptor (MR) antagonists (MRAs; spironolactone or eplerenone), or potassium-sparing diuretics (eg, amiloride) [6]. Recent studies have found that despite medical therapy, patients with PA remain at increased risk of cardiovascular events and renal failure [7, 8], leading to concerns regarding its efficacy. In addition, these investigators found that excess risk was only observed in patients with persistent renin suppression, suggesting that renin measurements during medical therapy may reflect adequacy of MR blockade [7, 8]. Prior to this, there has been a paucity of evidence on targets for adequate biochemical control, and some experts have suggested targeting a high-normal potassium level [9, 10]. Poor tolerance and adherence to medication may explain the poorer outcomes observed with medical therapy. Spironolactone, often the first-line medication, can lead to dose-dependent side effects such as gynecomastia and mastalgia (breast tenderness) [11]. While spironolactone is efficacious for hypertension [12] and resistant hypertension [13], it may be less well tolerated in patients with PA, who have higher aldosterone levels and potentially require higher doses, especially in unilateral PA [14].

Bilateral PA is treated with medications, but unilateral PA is curable with unilateral adrenalectomy. While unilateral PA may be equally well managed with long-term medications [15], current guidelines recommend adrenalectomy as it is curative [6], is more cost-effective in the long-term [16], and leads to better QOL [4]. However, there has not been any randomized controlled trial demonstrating the superior efficacy of surgery to medical therapy in unilateral PA. The main reason for this is that only patients seeking surgery undergo the invasive subtype test, adrenal vein sampling (AVS) [6]. As a result, the majority of patients with AVS-confirmed unilateral disease undergo surgery, precluding a direct comparison of surgical and medical therapy. However, some patients undergo medical therapy prior to surgery. This provides an opportunity to compare the efficacy of both modalities in the same patient.

In our study, we aimed to assess the long-term tolerability and efficacy of medical therapy in patients with PA in a large retrospective cohort study. We further compared the outcomes between patients with unilateral and bilateral PA. In the aforementioned group of patients undergoing a course of medical therapy before surgery, we also compared the efficacy of medical vs surgical therapy.

Methods

In our study, we included patients diagnosed with PA and managed on medications, which were spironolactone, eplerenone, and amiloride. We included all patients satisfying these criteria who were on follow-up at our 2 tertiary centers (Changi General Hospital and Singapore General Hospital) from year 2000 to 2020. We defined a diagnosis of PA in accordance with the Endocrine Society guidelines [6]. In our centers, we screened for PA using plasma aldosterone concentration (PAC) and plasma renin activity (PRA). Prior to that, we discontinued antihypertensives that interfere with the renin-angiotensin-aldosterone system for at least 2 weeks in most patients, and discontinued potassium-sparing diuretics for at least 6 weeks in all patients. Patients with precedent hypokalemia were prescribed potassium supplementation to aim for serum potassium of at least 3.5 mmol/L before baseline aldosterone was measured. In both centers, we confirmed the diagnosis of PA using the intravenous saline infusion test (SLT), and all patients had a post-SLT PAC at least 140 pmol/L. Clinical data were obtained as described in our

prior study on this cohort [17] and include baseline demographics and pretreatment PAC and PRA. We excluded patients treated with adrenalectomy only and not started on medical therapy, prescribed medical therapy for less than 4 weeks before adrenalectomy, or those on medical therapy for less than 3 months.

Subtyping

In both centers, adrenal vein sampling (AVS) was done sequentially under continuous cosyntropin infusion, with a cortisol gradient of >5 used to determine successful cannulation. Unilateral PA was determined by a lateralization ratio of >4, taken as the aldosterone-to-cortisol ratio of the higher adrenal vein divided by the contralateral side. Lateralization <2 was consistent with bilateral PA, while lateralization ratios between 2 and 4 were discussed at a multidisciplinary meeting for final decision regarding surgery [17]. Some patients without successful AVS proceeded with surgery based on evidence of contralateral suppression (aldosterone-to-cortisol ratio of contralateral vein less than peripheral), or computed tomography (CT) findings of a unilateral adenoma and normal contralateral adrenal. In patients with available results, we assessed patients after adrenalectomy using the Primary Aldosteronism Surgery Outcome (PASO) criteria [18] for clinical and biochemical outcomes.

Since not all patients underwent subtype testing, we also applied a clinical prediction score, the aldosterone-potassium ratio (APR) [17], to identify patients with likely unilateral PA. We previously developed the APR in our Asian cohort, and successfully validated it in a European cohort. APR is calculated using baseline serum aldosterone (ng/dL) divided by lowest-ever potassium level (mmol/L). Patients with an APR >10 have an 84.4% likelihood of having unilateral PA. For this study, we classified patients with indeterminate subtype (no AVS done or failed AVS) with APR >10 as unilateral PA. Patients treated with long-term medical therapy were analyzed separately from those patients who were treated with medical therapy prior to surgery.

Medical Therapy and Side Effects

Patients managed with medical therapy were started on either spironolactone, eplerenone, or amiloride based upon physician and patient preference. Serum potassium and creatinine were monitored within the first 4 weeks from initiation of medications, and after each dose titration. Hyperkalemia was defined as a rise in a serum potassium level above 5.0 mmol/L. Significant rise in creatinine was defined as a rise in serum creatinine of >30% which led to a decrease or cessation of medication by the managing physician. Starting doses were usually spironolactone 25 mg, eplerenone 50 mg, and amiloride 5 mg daily, with dose adjustments made every 4 to 12 weeks. Medical therapy was titrated with the aim of controlling hypertension while reducing other antihypertensive medications. The aim was also to achieve normokalemia without the use of potassium supplementation in all patients, although some physicians additionally targeted a high-normal serum potassium of 4.3 mmol/L or greater [10]. In patients with adequate control of potassium but persistent hypertension, additional antihypertensive medications were added. Plasma renin activity (PRA) measurements were done at the discretion of each physician, with the aim of achieving a release from renin suppression (PRA >1 ng/mL/h). During medical therapy, patients were monitored for side effects of medications, including gynecomastia, breast pain, decreased libido, menstrual irregularity, hypotension, and gastrointestinal intolerance. In the event of side effects, medications were either continued, doses reduced, switched to an alternative, or stopped altogether, based upon physician and patient choice. The highest dose of each medication prescribed was recorded, as well as the final tolerated dose. Incidences of severe hypokalemia (<3.0 mmol/L) or severe hyperkalemia (>6.0 mmol/L) while on medical therapy were also noted.

Assessment of Efficacy

Our primary outcome was to evaluate efficacy of medical therapy based on clinical (blood pressure) and biochemical (PRA and potassium) control. Clinic blood pressure readings and serum potassium results were recorded during each year of follow-up, and the average readings used for analysis. PRA was taken from the most recent clinic follow-up for those on medical therapy. Clinic BP measurements were taken using an automated BP monitor after 5 minutes of rest. Adequate clinical control was defined as BP <140/90 mmHg. Biochemical control was defined as the ability to achieve high-normal serum potassium levels ≥4.3 mmol/L (midpoint of reference range, 3.5-5.0 mmol/L), as well as unsuppressed PRA levels (>1 ng/mL/h). Patients who still required potassium supplements were designated a serum potassium level of 3.2 mmol/L, consistent with persistent hypokalemia.

Statistical Analysis

Statistical analysis was conducted using SPSS version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as a mean (SD) or median (interquartile range) and analyzed using the independent *t* test or McNemar test as appropriate. Categorical variables were expressed as number

(percentage) and compared using the chi-squared test for significance. Comparisons between efficacy and side effects in unilateral and bilateral PA were made. In patients with unilateral PA who were initially treated with medications and then underwent surgery, we compared clinical and biochemical outcomes after medical and surgical therapies, using paired *t* test and chi-square test. All statistical tests were 2-tailed and $P < 0.05$ was considered significant.

Results

Of 274 patients with PA managed at 2 referral centers from 2000 to 2020, 155 patients with PA were treated with long-term medical therapy (Fig. 1). The median age was 56 (49-64) years, and 52 (35.5%) were female. Seventy-six patients on long-term medical therapy were classified as having unilateral PA using AVS, CT, and APR clinical prediction score. The remaining 79 patients were classified as bilateral PA. At baseline, patients with unilateral PA had higher PAC ($P < 0.001$) and lower lowest-recorded potassium levels ($P < 0.001$) (Table 1). We also conducted a separate analysis on 46 patients with unilateral PA (determined by AVS or CT) who underwent surgery and were treated with medical therapy prior to surgery (detailed later).

Efficacy

Among those on long-term medical therapy, 57.4% of patients achieved controlled BP <140/90 mmHg and 90.1% achieved normokalemia (48.0% achieved potassium ≥4.3 mmol/L) (Table 2). In addition, 55.5% achieved normotension and normokalemia (30.3% achieved normotension with potassium ≥4.3 mmol/L) (Fig. 2). Among 57 patients who had PRA measurements done during medical therapy, 36 (63.2%) achieved unsuppressed renin of PRA ≥1 ng/mL/h. In addition, 61.4% achieved controlled BP, 33.3% achieved both potassium ≥4.3 mmol/L and PRA ≥1 ng/mL/h, and only 24.6% achieved all 3 stringent targets. Seventeen patients had PRA >1 ng/mL/h but potassium <4.3 mmol/L, while 12 patients had potassium ≥4.3 mmol/L but PRA <1 ng/mL/h. Hence, concordance of biochemical control as measured using potassium and renin was seen in only 28 of 57 (49.1%) patients. Patients

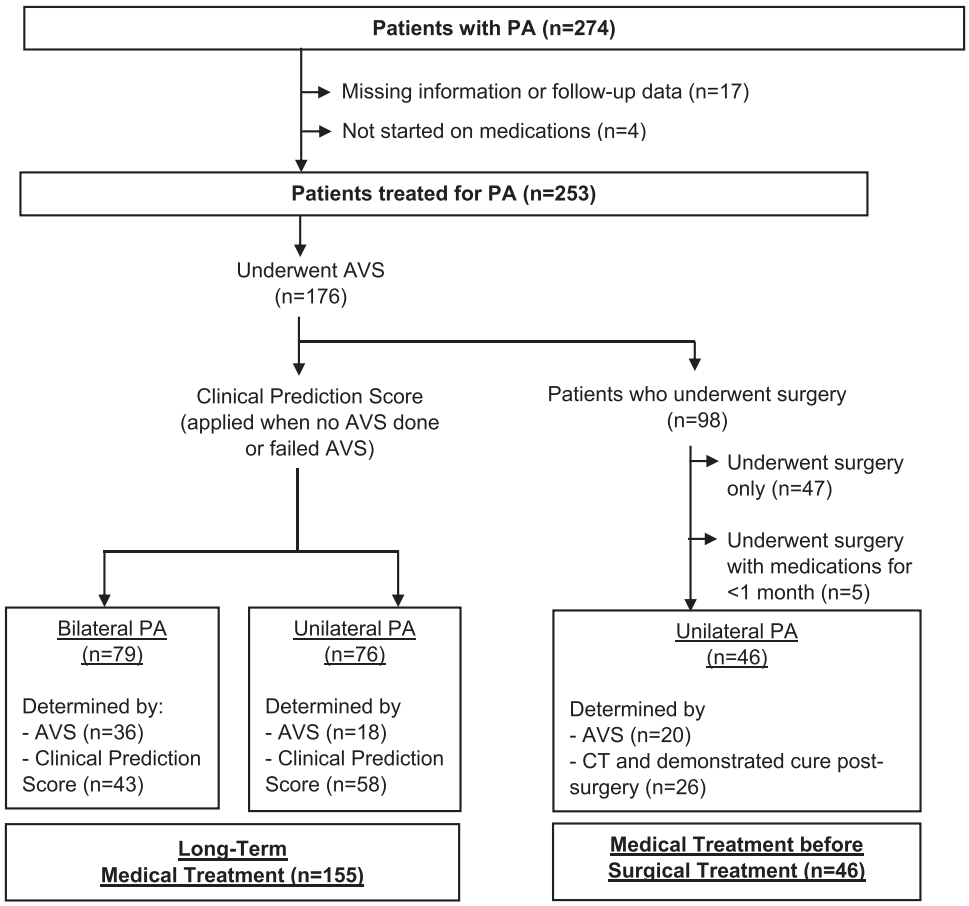

Figure 1. Flow chart for 155 patients with primary aldosteronism (PA) with long-term medical treatment included in the study; 46 patients with >1 month course of medical treatment before surgery for secondary analysis. Abbreviations: AVS, adrenal vein sampling; CT, computed topography; PA, primary aldosteronism.

Table 1. Baseline demographics of 155 patients with primary aldosteronism treated with medications

	Unilateral (medications only) (N = 76)	Bilateral (medications only) (N = 79)	Total (medications only) (N = 155)	*P*
Age (years)	54.5 (49.0–63.0)	56.0 (49.0–64.0)	56.0 (49.0–64.0)	0.55
Female	24 (31.6%)	28 (35.4%)	52 (35.5%)	0.61
Ethnicity				
Chinese	63 (82.9%)	63 (79.7%)	126 (81.3%)	0.39
Malay	8 (10.5%)	7 (8.9%)	15 (9.7%)	
Indian	2 (2.6%)	7 (8.6%)	9 (5.8%)	
Others	3 (3.9%)	2 (2.5%)	5 (3.2%)	
Body mass index (kg/m^2)	25.3 (23.3–28.1) N = 68	25.7 (23.6–28.2) N = 77	25.6 (23.4–28.1) N = 145	0.73
Systolic BP, mmHg	150.0 (135.1–164.8)	152.0 (140.5–160.0)	150.5 (139.0–162.0)	0.55
Diastolic BP, mmHg	82.8 (80.0–94.0)	84.0 (80.0–91.5)	84.0 (80.0–92.5)	0.96
Smoking	17/62 (27.4%)	7/63 (11.1%)	24/125 (19.2%)	0.15
Defined daily dose of antihypertensive medications	2.3 (1.5–4.1)	2.0 (1.0–3.6)	2.0 (1.3–3.7)	0.13
Lowest serum potassium (mmol/L)	2.6 (2.3–2.9) N = 76	3.0 (2.7–3.3) N = 76	2.8 (2.5–3.0) N = 152	<0.001
Estimated GFR (ml/min/1.73m ^{2})	80.7 (66.9–96.4) N = 75	79.9 (68.7–96.6) N = 79	80.3 (68.0–96.4) N = 154	0.73
Baseline PAC (ng/dL)	1056 (833–1376) N = 76	589 (443–700) N = 76	744 (547–1135) N = 152	<0.001
Baseline PRA (ng/mL/h)	0.22 (0.20–0.55) N = 75	0.30 (0.20–0.60) N = 79	0.25 (0.20–0.60) N = 154	0.48
Duration of hypertension (yrs)	8.0 (5.0–11.3) N = 58	10.0 (3.0–17.0) N = 59	9.0 (4.0–15.0) N = 117	0.56
Ischemic heart disease	5 (6.6%)	8 (10.1%)	13 (8.4%)	0.43
Stroke	9 (11.8%)	7 (8.9%)	16 (10.3%)	0.54
Hyperlipidemia	41 (53.9%)	44 (55.7%)	85 (54.8%)	0.83
Diabetes	26 (34.2%)	29 (36.7%)	55 (35.5%)	0.75
Atrial fibrillation	6/75 (8.0%)	3/79 (3.8%)	9/154 (5.8%)	0.27
CT findings				
Unilateral adenoma	47/71 (66.2%)	43/76 (56.6%)	90/147 (61.2%)	0.33
Bilateral abnormal	5/71 (7.0%)	4/76 (5.3%)	9/147 (6.1%)	
Bilateral normal	19/71 (26.8%)	29/76 (38.2%)	48/147 (32.7%)	
Medication				
Spironolactone	69 (90.8%)	71 (89.9%)	140 (90.3%)	0.62
Eplerenone	7 (9.2%)	7 (8.9%)	14 (9.0%)	
Amiloride	0 (0.0%)	1 (1.3%)	1 (0.6%)	

Data are median (interquartile range) or number (percent). Defined daily dose using WHO classification (https://www.whocc.no/atc_ddd_index/).
Abbreviations: BP, blood pressure; CT, computed tomography; GFR, glomerular filtration rate; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity.

with unsuppressed renin (PRA ≥1 ng/mL/h) were more likely to have controlled hypertension than those with persistent renin suppression (72.2% vs 42.9%; P = 0.028) (Supplementary Table 1) [19].

The majority of patients, 140 of 155 (90.3%), were started on spironolactone as the first-line treatment. Patients with unilateral PA were prescribed a higher daily dose of spironolactone, 57 (41-119) mg, compared with patients with bilateral PA, 50 (25-50) mg, P < 0.001 (Table 2). However, due to side effects, the final tolerable dose of spironolactone was lower and similar in both groups, at 25 (0-72) mg and 25 (0-50) mg respectively (P = 0.37).

The clinical response in patients with both unilateral and bilateral PA were similar in terms of proportion with controlled BP, and absolute decline of systolic BP (−14.3 and −14.2 mmHg; P = 0.92) and diastolic BP (−7.6 vs −6.8 mmHg; P = 0.88), respectively (Table 2). A similar proportion of patients with unilateral PA were able to achieve a potassium ≥4.3 mmol/L compared with bilateral PA (40.5% vs 55.1%; P = 0.072), with similar numbers having persistent hypokalemia (13.5% vs 6.4%; P = 0.14). The proportion of patients with PRA ≥1 ng/mL/h was similar in both unilateral and bilateral groups (57.9% vs 65.8%; P = 0.56).

Tolerance

A total of 52.3% (81 of 155) patients experienced at least 1 adverse effect on medical therapy (Table 2 and Fig. 2). Side effects were more common in patients with unilateral PA compared with bilateral PA (63.2% vs 41.8%; P = 0.008), and patients using spironolactone, 90 of 184 (48.9%), compared with 1 of 26 (3.8%) patients using eplerenone, and 1 of 11 (9.1%) patients using amiloride (P < 0.001). There was a higher incidence of side effects in male patients, 61 of 103 (59.2%), compared with female patients, 20 of 52 (38.5%) (P = 0.015), which was largely contributed by anti-androgenic side effects (Fig. 2). Common side effects included a rise in either potassium or creatinine in 32.1% of patients, and anti-androgenic side effects in 33.7% of male patients. Other side effects included hypotension, hyponatremia, gastrointestinal symptoms, headache, tachycardia, and somnolence.

Side effects were also more common with longer duration of medical therapy, (57.9% in those using >12 months vs 27.6% for those using ≤12 months; P < 0.003). Side effects resulted in a reduction of dose in 35 (25.0%) patients, change of medication in 16 (11.4%) patients, and complete cessation of medical therapy in 17 (12.9%) patients (Table 2).

The median final tolerable dose among patients prescribed spironolactone was 25 mg, and side effects were related to dose of spironolactone (Table 3). Patients on higher doses (>50 mg) were more likely to have hyperkalemia compared with those on lower doses (≤50 mg) (36.8% vs 10.8%; P < 0.001) and were also more likely to cause sexual side effects in males (48.6% vs 23.1%; P = 0.012). Gastrointestinal side effects were more common in patients

Table 2. Efficacy and tolerance of medications in patients with unilateral and bilateral primary aldosteronism

	Unilateral PA (N = 76)	Bilateral PA (N = 79)	Total (N = 155)	*P*
Post-treatment SBP, mmHg, N = 151	136.5 (128.7–144.5)	136.0 (127.2–145.0)	136.0 (128.0–144.6)	0.82
Post-treatment DBP, mmHg, N = 152	76.8 (73.0–85.4)	78.2 (73.5–83.7)	77.3 (73.3–84.6)	0.98
Change in SBP, mmHg, N = 151	−14.3 (−28.3 to 2.4)	−14.2 (−25.4 to −2.0)	−14.2 (−25.7 to 0.3	0.92
Change in DBP, mmHg, N = 152	−7.6 (13.9 to 2.1)	−6.8 (−12.9 to 0.8)	−7.4 (−13.3 to 2.0)	0.88
BP controlled (<140/90 mmHg)	45 (59.2%)	44 (55.7%)	89 (57.4%)	0.66
Post-treatment potassium, mmol/L, N = 152	4.2 (3.9–4.4)	4.3 (3.9–4.5)	4.3 (3.9–4.5)	0.12
Normokalemia (≥3.5mmol/L) without supplementation	64/74 (86.55%)	73/78 (93.6%)	137/152 (90.1%)	0.14
Potassium ≥4.3 mmol/L	30/74 (40.5%)	43/78 (55.1%)	73/152 (48.0%)	0.072
PRA ≥1 ng/mL/h	11/19 (57.9%)	25/38 (65.8%)	36/57 (63.2%)	0.56
Highest spironolactone dose, mg/day,	57 (41–119)	50 (25–50)	50 (25–100)	<0.001
Final spironolactone dose, mg/day	25 (0–71.875)	25 (0–50)	25 (0–50)	0.37
Side effects	48 (63.2%)	33 (41.8%)	81 (52.3%)	0.008
Action taken				
No action	36 (47.4%)	51 (64.6%)	87 (56.1%)	0.011
Decreased dose	24 (31.6%)	11 (13.9%)	35 (22.6%)	
Change to eplerenone or amiloride	5 (6.6%)	11 (13.9%)	16 (10.3%)	
Stopped medications	11 (14.5%)	6 (7.6%)	17 (11.0%)	
Duration of medical therapy, yr	4.5 (2–11)	3 (2–6)	3 (2–9)	0.019

Data are median (interquartile range) or number (percent). Abbreviations: DBP, diastolic blood pressure; PA, primary aldosteronism; PRA, plasma renin activity; SBP, systolic blood pressure.

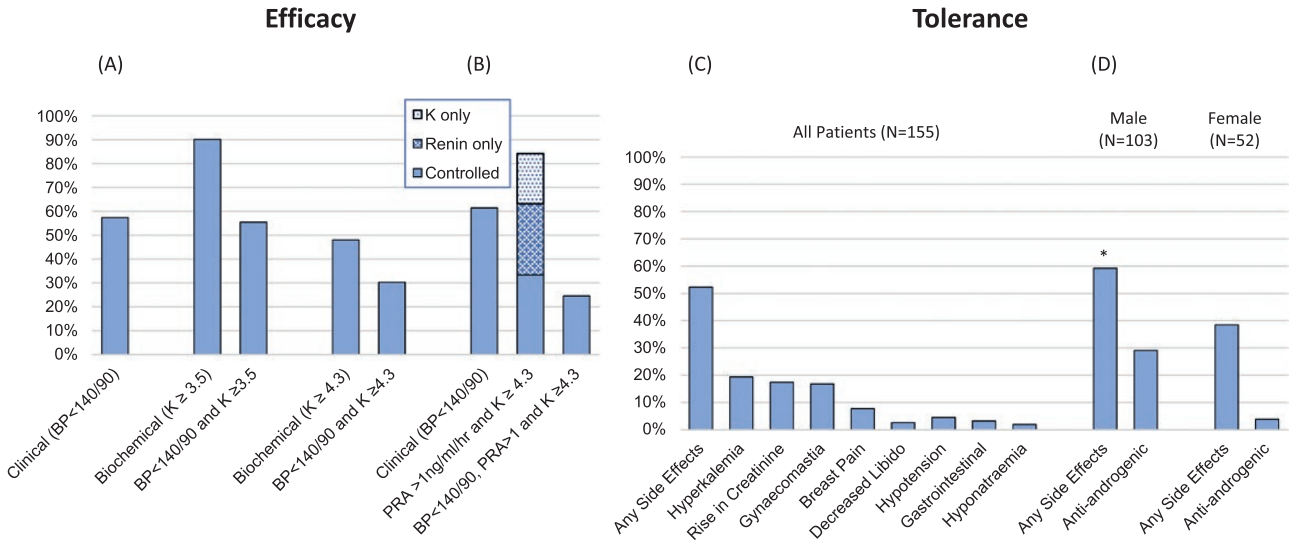

Figure 2. Efficacy of medical treatment to achieve clinical (blood pressure <140/90 mmHg) and biochemical control (serum potassium ≥3.5 mmol/L or serum potassium ≥ 4.3 mmol/L, and plasma renin activity ≥1 ng/mL/h) in (A) all patients, and (B) patients with plasma renin activity measured while on medical treatment (n = 57). Tolerance as assessed by side effects in (C) all patients, and (D) stratified by gender. Abbreviations: BP, blood pressure; K, potassium; PRA, plasma renin activity. **P* < 0.05 compared with female gender.

on lower doses of spironolactone, and this was possibly because the side effects limited further increase in dose. When stratified by the final tolerable spironolactone dose, patients who were tolerating higher doses (>50 mg) had more severe phenotype at baseline, with higher PAC and higher baseline systolic and diastolic BP (Supplementary Table 2) [19]. While post-treatment BP was higher in those prescribed higher spironolactone doses, the change in systolic BP and diastolic BP was similar in both groups, with a mean drop in systolic BP of 14.8 (2.3 to 27.8) mmHg and diastolic BP of 7.5 (−1.5 to 13.5) mmHg.

While on medical treatment, 7 patients experienced severe hypokalemia (≤2.5 mmol/L) due to nonadherence to medications, 1 patient suffered a cerebellar stroke from a hypertensive crisis, and another patient developed an atrioventricular block (Supplementary Table 3) [19]. Another 4 patients had severe hyperkalemia (≥6.0 mmol/L) requiring admission for treatment, which required reduction or cessation of medical treatment altogether. Of 33 patients who experienced hyperkalemia, 5 patients had a low-normal potassium <4.3 mmol/L at the final clinic visit.

Comparison of Medical and Surgical Therapy in Unilateral PA Patients

Forty-six patients with unilateral PA underwent surgery after an initial course of medical therapy (median age 51 years, 39.1% female) (Supplementary Table 4) [19]. Compared with patients with unilateral PA on long-term medications, patients who underwent surgery were younger, had a higher diastolic BP, lower baseline PRA, and were more likely to harbor a unilateral adrenal adenoma. These patients used a higher final median spironolactone dose of 62.5 (25-100) mg daily, but only 67.4% achieved normokalemia (Supplementary Table 5) [19]. We compared the clinical response after surgery to initial medical therapy. Systolic BP improved significantly from 157 ± 17 to 141 ± 16 mmHg after medications ($P < 0.001$) and declined further to 135 ± 17mmHg after surgery ($P = 0.045$). Diastolic BP similarly improved from 92 ± 11 to 85 ± 10 mmHg after medical therapy ($P < 0.001$) and declined further to 79 ± 8 mmHg after surgery ($P = 0.002$) (Fig. 3). Of note, 2 patients included in this group had persistent hypokalemia after adrenalectomy and medical treatment was reinitiated after surgery. One patient had lateralization on AVS, while the other patient had undergone surgery based on CT findings alone. Patients who underwent surgery based on AVS lateralization had similar clinical response to those who underwent surgery without a successful AVS.

Discussion

We found in our large cohort of patients with PA treated with long-term medications that although a large majority (90%) achieved normokalemia without potassium supplementation, only about half achieved clinical control of hypertension (<140/90 mmHg), or biochemical control (if a high-normal potassium or unsuppressed renin were targeted). 52% of patients experienced side effects to medications, which resulted in dose reduction or cessation of medications in a third of patients. Recent studies have

Table 3. Side effects stratified by highest prescribed dosage of spironolactone

	≤ 50 mg daily (N = 83)	> 50 mg daily (N = 57)	Total (N = 140)	*P*
All side effects	41 (49.4%)	40 (70.2%)	81 (57.9%)	0.014
Electrolyte derangements	20 (24.1%)	25 (43.9%)	45 (32.1%)	0.014
Hyperkalemia	9 (10.8%)	21 (36.8%)	30 (21.4%)	<0.001
Rise in creatinine	14 (16.9%)	13 (22.8%)	27 (19.3%)	0.38
Anti-androgenic side effects (male)	12/52 (23.1%)	18/37 (48.6%)	30/89 (33.7%)	0.012
Gynecomastia	9/52 (17.3%)	16/37 (43.2%)	25/89 (28.1%)	0.007
Breast pain	7/52 (13.5%)	4/37 (10.8%)	11/89 (12.4%)	0.71
Decreased libido	1/52 (1.9%)	3/37 (8.1%)	4/89 (4.5%)	0.17
Mastalgia (female)	0/31 (0.0%)	1/20 (5.0%)	1/51 (2.0%)	0.21
Hypotension	5 (6.0%)	2 (3.5%)	7 (5.0%)	0.50
Hyponatremia	2 (2.4%)	1 (1.8%)	3 (2.1%)	0.79
Gastrointestinal intolerance	5 (6.0%)	0 (0.0%)	5 (3.6%)	0.059
Others	2 (2.4%)	3 (5.3%)	5 (3.6%)	0.37
Action taken				
No action	46 (55.4%)	26 (45.6%)	72 (51.4%)	<0.001
Decreased dose	11 (13.3%)	24 (42.1%)	35 (25.0%)	
Change to eplerenone or amiloride	13 (15.7%)	3 (5.3%)	16 (11.4%)	
Stopped medications	13 (15.7%)	4 (7.0%)	17 (12.9%)	

Data are presented as number (percent).

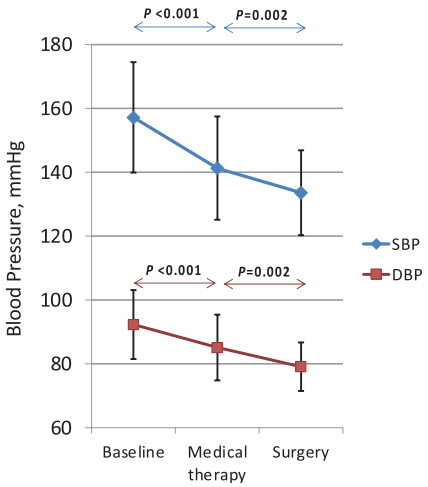

Figure 3. Change in blood pressure in 46 patients with unilateral primary aldosteronism treated initially with medical therapy before undergoing adrenalectomy. Blood pressure presented as mean (SD) and compared with paired *t* test. Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

found that medical treatment failed to ameliorate the excess cardiovascular risks of PA [7, 8, 20] and our findings suggest that the maximal tolerated dose in many patients may be inadequate for control of PA itself. In patients with unilateral PA, despite requiring higher medication doses, they were more likely to lack biochemical control. In our direct comparison of medical therapy and surgery in patients with unilateral PA, we found that surgery further improved BP and potassium control beyond what was achievable by the initial course of medical therapy. This further highlights the importance of subtype differentiation in PA, as well as the advantage of adrenalectomy for unilateral PA.

Patients with PA often have more severe or resistant hypertension than patients with essential hypertension. This may explain why many of our PA patients continued to have uncontrolled hypertension on medical treatment [1, 21]. Medical therapy provided an overall decrease in BP of 16/7 mmHg. Persistent hypertension may partially explain the unabated cardiovascular risk observed with medical therapy [7, 20], but biochemical control is important as well since hyperaldosteronism has harmful cardiovascular effects. While there is currently a PASO consensus for assessing biochemical resolution after unilateral adrenalectomy (normalization of aldosterone-renin ratio and hypokalemia) [18], there is currently no equivalent consensus for patients on medical therapy.

All patients on medical therapy for PA should achieve normokalemia without further potassium supplementation (achieved in 90% of our patients) but some experts also recommend targeting a high-normal potassium level [10], which only 45% achieved. This could be due to not all clinicians targeting this threshold, or difficulty to achieve this due to medication side effects. Some experts also suggest attaining PRA >1 ng/mL/h, to demonstrate reversal of the sodium overload state and release of renin suppression that is the hallmark of PA [22]. This was supported by recent studies demonstrating reduced cardiovascular and renal events in patients on medications when PRA was >1 ng/mL/h [7, 8, 20]. However, there is currently no prospective study demonstrating that achieving such a level leads to

improved outcomes. Only 60% of our patients achieved PRA >1 ng/mL/h, and only a third achieved both PRA >1 ng/mL/h and potassium ≥4.3 mmol/L. Looking into the possible reasons, PRA may be affected by factors such as sodium intake [23], hydration status, and medication use. Four of our 10 patients with suppressed PRA were on beta-blocker treatment which may explain the persistent renin suppression. It has also been argued that one-third of all patients with essential hypertension have low-renin hypertension [9, 24] and targeting unsuppressed renin may not be ideal. In view of these confounders to PRA acting as a measure of PA control, new prospective studies should be done to evaluate if titration of medical therapy to release renin suppression leads to improved outcomes. Until then, it may remain more feasible to use potassium to guide dose titration as it is more widely available, cheap, practical, and less prone to biological and assay variability. In patients with persistent renin suppression but high-normal potassium levels, further dose escalation of MRA may be difficult due to concerns of hyperkalemia.

Almost half of our cohort experienced at least 1 side effect with medications, and this was more common with longer duration of treatment, male patients, spironolactone use, and higher dosage. In addition, adherence is an important issue with long-term medical therapy. Seven of our patients had severe hypokalemia due to missed medications, with 1 experiencing a hypertensive crisis and resultant stroke. Common side effects of medication include hyperkalemia and anti-androgenic effects in male patients, which were both dose-related. Hyperkalemia occurred in 17.4% of our patients, with 4 patients having severe hyperkalemia (>6.0 mmol/L). There were also several patients with progressive renal impairment where hyperkalemia necessitated cessation of medical therapy. These factors highlight the need for close monitoring of potassium. As for anti-androgenic side effects, gynecomastia occurred in 22% of our patients receiving low dose (≤50 mg) spironolactone, and 30% overall. This is consistent with a recent trial, whereby 36% of patients switched to eplerenone due to side effects with spironolactone [25]. Most of our patients were initially started on spironolactone, with less frequent usage of eplerenone due to its higher cost.

While spironolactone doses of 50 mg are generally sufficient for patients with essential hypertension [12], higher doses occasionally required in PA may be less tolerated [25, 26]. This was particularly evident in our patients with unilateral PA who had a more severe phenotype. Furthermore, among the patients who proceeded with surgery after initial medical therapy, surgery led to better BP and potassium control than medications. While the purpose of medications before surgery was likely to improve BP and potassium, and not to attain complete control, it is notable that despite a median spironolactone dose of 62.5 mg daily, almost a third (32.6%) still had hypokalemia. There has not been any randomized controlled trial comparing the efficacy of medical and surgical treatment in patients with unilateral PA, and this is unlikely to occur since patients who undergo AVS usually opt for surgery. Our crossover design allowed us a within-patient comparison of the 2 therapies, albeit these patients had shorter duration of medical therapy than patients with bilateral PA. Our results further support the importance of subtyping and adrenalectomy surgery for patients with unilateral PA. Other arguments in support of adrenalectomy include long-term cost-effectiveness [16], and better QOL [4]. Further arguments against medical therapy include the idea that patients with PA may co-secrete glucocorticoids which may increase the risk of diabetes mellitus [27]. Since MRAs do not antagonize the glucocorticoid receptor, this may further explain the poorer outcomes with medical therapy. Overall, it would appear that surgery is a better therapeutic option for patients with unilateral PA as recommended by current guidelines [6].

Moving forward, it may be prudent to consider other classes of medical therapy beyond the MRAs currently available. We do not routinely monitor serum aldosterone in patients on medical therapy, but MRAs competitively inhibit the MR receptor which leads to a paradoxical rise in aldosterone levels [28]. This persistent hyperaldosteronic state may potentially be harmful via nongenomic mechanisms not regulated by the MR which is targeted by MRAs [29]. There are several aldosterone synthase inhibitors currently being developed, although there were concerns about lack of specificity for aldosterone synthase, and risk of adrenal insufficiency with one [30]. There has also been evidence that macrolides can reduce aldosterone production in aldosterone-producing adenomas that harbor the most common somatic mutation, *KCNJ5* [31], and there is currently an ongoing clinical trial to assess if this may be a potential therapeutic option [32].

Despite being one of the largest studies looking at the long-term tolerance and efficacy of medical therapy in PA, we recognize several limitations in our study. First, being a large multicenter retrospective study, diagnostic protocols were similar between practicing clinicians but treatment algorithms for medication titration or assessment for side effects may have differed, reflecting the realities of clinical practice. Second, not all patients who underwent surgery had prior AVS-proven lateralization. This may have led to an underestimation of clinical improvement after surgery if some patients had underlying bilateral PA. However, this is unlikely to change our conclusion as we have already found surgery superior to medical therapy. Third, renin measurements were only made in a third of our patients on long-term medications

as this is not part of prevailing guidelines. Nevertheless, there were no other differences between patients with renin measurements and those without (data not presented). More importantly, our findings highlight the discordance between renin and potassium when used to assess biochemical control. Further prospective studies should be done to evaluate which is a better strategy, with assessment for hard endpoints such as incidence of cardiovascular events. Fourth, our cohort of 201 patients treated for PA over 2 decades likely only represents a small percentage of all patients with PA [33, 34], as many patients with hypertension fail to be screened and diagnosed for PA. This highlights the need for greater awareness of PA among clinicians. Finally, most of our patients on medical therapy were on spironolactone and we could not compare it with alternatives like eplerenone or amiloride. Studies have found spironolactone to be more or equally efficacious to eplerenone [26, 35], but this was not the aim of our study. In view of its lower cost and good efficacy, spironolactone is currently our first-line medical therapy option, but as shown in our study, its use can be limited by its side effects profile.

Conclusion

Although medical therapy improves hypertension and biochemical control in patients with PA, side effects are common, and this can limit the overall efficacy of medications. Alternatives to current medical therapy options may help to address this. In patients with unilateral PA, our study supports the concept that surgery would be a better first-line treatment option compared to medical therapy.

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