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Research

Effect of the Adrenalectomy and Mineralocorticoid Receptor Antagonists on the Clinical and Biochemical Outcomes in Patients with Primary Aldosteronism: A Single-center Experience

Primer Hiperaldosteronizmli Hastalarda Adrenalektomi ve Mineralokortikoid Reseptör Antagonist Tedavinin Klinik ve Biyokimyasal Sonuçlara Etkisi: Tek Merkez Deneyimi

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ABSTRACT

Objective: Primary hyperaldosteronism (PA) is a disorder in which non-suppressible hypersecretion of aldosterone from the adrenal gland. Treatment with either mineralocorticoid receptor antagonists (MRA) or unilateral adrenalectomy (ADX) of PA resolves hypokalemia, lowers blood pressure and ameliorates the parameters of impaired cardiac and renal function but may paradoxically result in a decline in estimated glomerular filtration rate (eGFR). This study compared the effects of ADX and MRA on clinical and biochemical outcomes in patients with PA.

Methods: Sixty-two patients with PA were recruited for this study. The patients were divided into two groups according to the PA treatment method. Group 1 (n=40) was defined as patients treated with MRA, and group 2 (n=22) was defined as patients who underwent ADX. Groups were compared in terms of creatinine, eGFR, potassium, sodium, plasma aldosterone concentration (PAC), plasma renin activity (PRA), aldosterone/renin ratio (ARR), presence of hypertension, and the percentage change in creatinine, eGFR, potassium, sodium. The correlation analysis between the percentage change in eGFR and the percent change of potassium with clinical and laboratory parameters was also performed.

Results: The mean age of the whole study group was 54.0±9.9 years. All patients had hypertension at baseline, and 11 patients (50%) had complete clinical success with hypertension without antihypertensive drugs after the treatment with ADX. Forthy-one patient had hypokalemia at baseline, and all of them resolved after the treatment with MRA or ADX. PAC, ARR, patients with hypokalemia, the percent change in eGFR and potassium were significantly higher in group 2 than in group 1 ($p<0.001$, $p=0.006$, $p=0.011$, $p=0.031$, and $p<0.001$; respectively). Significant positive correlations were observed between the percent change in eGFR and the percent change of potassium with PAC and ARR in the whole study group.

Conclusion: ADX could provide more benefit to renal function and resolve hypertension than the treatment of MRA. Aldosterone-induced glomerular hyperfiltration in PA resolves after both treatments and results in a more prominent decline in eGFR. Therefore, physicians should reevaluate the renal function after the treatments because pretreatment eGFR alone may not be a good predictor of renal function.

Keywords: Primary hyperaldosteronism, mineralocorticoid receptor antagonist, unilateral adrenalectomy, estimated glomerular filtration rate

ÖZ

Amaç: Primer hiperaldosteronizm (PA), adrenalden baskılanamayan aşırı aldosteron salgılanması ile karakterize bir hastalıktır. Uygun olmayan şekilde yüksek aldosteron üretimi, hipertansiyona, kardiyovasküler hasara, böbrek hasarı gelişimine ve hipokalemiye neden olmaktadır. PA'nın mineralokortikoid reseptör antagonistleri (MRA) veya tek taraflı adrenalektomi (ADX) ile tedavisi hipokalemiyi giderir, kan basıncını düşürür ve bozulmuş kardiyak ve renal fonksiyon parametrelerini iyileştirir, ancak paradoksal olarak tahmini glomerüler filtrasyon hızında (eGFR) bir düşüşe neden olabilir. PA ile ilgili güncel kılavuzlar, ADX'in MRA ile tıbbi tedaviye üstünlüğünü gösteren çalışmalardan dolayı tek taraflı aldosteron

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salgılayan adenomlar için ADX'i önermektedir. Bu çalışmada, PA'lı hastalarda ADX ve MRA'nın klinik ve biyokimyasal sonuçlar üzerindeki etkilerinin karşılaştırılması amaçlandı.

Gereç ve Yöntem: 2015-2021 yılları arasında PA tanısı alan hastaların tıbbi kayıtları incelendi. Altmış iki hastaya PA teşhisi konuldu ve belgelenmiş uzun vadeli takip verileri olan hastalar çalışmaya dahil edildi. Hastalar PA tedavi yöntemine göre iki gruba ayrıldı. Grup 1 (n=40) MRA ile tedavi edilen hastalar, grup 2 (n=22) ADX uygulanan hastalar olarak tanımlandı. Gruplar arasında kreatinin, eGFR, potasyum, sodyum, plazma aldosteron konsantrasyonu (PAC), plazma renin aktivitesi (PRA), aldosteron/renin oranı (ARR), hipertansiyon varlığı ve kreatinin, EGFR, sodyum, potasyum değişim yüzdeleri açısından karşılaştırıldı. eGFR değişim yüzdesi ve potasyumun değişim yüzdesi ile klinik ve laboratuvar parametreleri arasında korelasyon analizi de yapıldı.

Bulgular: Tüm çalışma grubunun yaş ortalaması 54,0±9,9 yıl idi. Tüm çalışma grubunda ortalama PAC ve PRA seviyeleri sırasıyla 40,6±36,6 ng/dL ve 0,34±0,22 ng/mL/saat olarak saptandı. Tüm hastalarda başlangıçta hipertansiyon vardı ve 11 hastada (%50) ADX ile tedaviden sonra antihipertansif ilaçlar olmaksızın hipertansiyonda tam klinik başarı elde edildi. Kırk bir hastada başlangıçta hipokalemi vardı ve hepsi MRA veya ADX ile tedaviden sonra düzeldi. PAC, ARR ve hipokalemisi olan hastalar grup 2'de grup 1'e göre anlamlı olarak daha yüksekti (sırasıyla p<0,001, p=0,006 ve p=0,011). Grup 2'deki eGFR, potasyum değişim yüzdesi grup 1'den anlamlı olarak daha büyüktü (sırasıyla p=0,031 ve p<0,001). Tüm çalışma grubunda eGFR değişim yüzdesi ve potasyum değişim yüzdesi ile PAC ve ARR arasında anlamlı pozitif korelasyonlar gözlendi.

Sonuç: ADX böbrek fonksiyonuna MRA tedavisinden daha fazla fayda sağlayabilir ve hipertansiyonu MRA tedavisinden daha fazla düzeltebilir. Ancak MRA tedavisi de özellikle ADX için aday olmayan hastalar için etkin bir tedavi seçeneği olarak düşünülebilir. PA'da aldosteron kaynaklı glomerüler hiperfiltrasyon, tedaviden sonra düzelir ve bu hastalarda daha belirgin bir eGFR düşüşü gözlenir. Bu nedenle, tedavi öncesi eGFR tek başına böbrek fonksiyonunun iyi bir göstergesi olmayabileceğinden, klinisyenler tedaviden sonra böbrek fonksiyonunu yeniden değerlendirmelidir.

Anahtar Kelimeler: Primer hiperaldosteronizm, mineralokortikoid reseptör antagonisti, unilateral adrenalektomi, tahmini glomerüler filtrasyon hızı

INTRODUCTION

Primary hyperaldosteronism (PA) is a group of disorders in which non-suppressible hypersecretion of aldosterone from the adrenal gland (1-3). Inappropriately elevated production of aldosterone in PA causes hypertension, cardiovascular damage, hypokalemia, and suppression of plasma renin. The most common causes of PA are bilateral idiopathic hyperaldosteronism (60 to 70 percent) and unilateral aldosterone-secreting adenomas (30 to 40 percent) (1,3). PA is estimated to be responsible for 5 to 13 percent of hypertension in the population and is the most common cause of secondary hypertension (1,3,4). Non-suppressing hypersecretion of aldosterone is currently increasingly diagnosed in patients with hypertension but is still an underdiagnosed cause of hypertension (3,4).

The importance of early identifying PA is not only due to its high prevalence but also because patients with PA have a higher risk of cardiovascular morbidity and mortality than patients with primary hypertension (5,6). Inappropriate aldosterone secretion influences cardiovascular disease as well as the effect on renal injury (7-9). Hyperaldosteronism may cause a higher estimated glomerular filtration rate (eGFR) and renal perfusion pressure independent of hypertension via activation of the mineralocorticoid receptor (3,7-9). Higher glomerular hyperfiltration is a functional abnormality in PA and masks the underlying structural renal damage due to the longstanding impact of excessive aldosterone secretion (3,7-11).

Specific treatments alleviate the significant adverse effects of PA on patient outcomes. Treatment with either mineralocorticoid receptor antagonists (MRA) or unilateral adrenalectomy (ADX) for PA resolves hypokalemia, decreases blood pressure and eases the parameters of impaired cardiac and renal function but may paradoxically result in a decline in eGFR (1,8). The medical treatment of PA with MRA is the treatment of choice for idiopathic hyperaldosteronism. Current clinical guidelines on PA recommend ADX for unilateral aldosterone-secreting adenomas based on the studies showing the superiority of ADX over the medical treatment with MR (1,11-16). Although not the optimal treatment choice, MRA may also be used to treat patients with unilateral aldosterone-secreting adenoma who are not a candidates for surgery (17). This study compared the effects of ADX and MRA on clinical and biochemical outcomes in patients with PA.

METHODS

This study was a cross-sectional and retrospective study. In this study, the medical records of the patients diagnosed with PA between 2015 and 2021 were reviewed. Sixty-two patients were diagnosed with PA and had documented long-term follow-up data (>1 year) were recruited for the study. Patients with chronic renal impairment, eGFR <60 mL/min/1.73 m^2, and patients with diabetes mellitus were excluded from the study. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula as published in 2009 (18).

Plasma aldosterone concentration (PAC) and plasma renin activity (PRA) were measured using available kits. PAC and PRA were determined via chemiluminescent immunoassay

technology. The diagnosis of PA was defined in patients with an aldosterone/renin ratio (ARR) of more than 20 and at least one positive result on the confirmatory tests (1). ADX was performed in patients with documented unilateral primary aldosteronism and had the lateralization of the source of the excessive aldosterone secretion. Patients with an age of under 35 years with spontaneous hypokalemia-marked aldosterone excess and unilateral adrenal lesions also underwent surgery even without adrenal venous sampling evaluation. The patient who was unable to undergo surgery was recommended medical treatment with mineralocorticoid antagonists. Spironolactone was started with a dose of 12.5 to 25 mg/d and was titrated to a maximum dose of 100 mg/day, if necessary.

The age and gender of the patients were recorded. Venous blood samples were drawn following overnight fasting. Creatinine, eGFR, potassium, sodium, PAC, PRA, and ARR were recorded at baseline and three months after the treatment with ADX or MRA. The lowest potassium level was recorded before treatment, and those with a serum potassium concentration <3.5 mmol/L were considered hypokalemia.

The percent change of creatinine, eGFR, sodium, and potassium between the levels at pretreatment and the levels three months after the treatments (ADX or MRA) was calculated as [(the level at pretreatment-the level at the third month of treatment)/the level at pretreatment] ×100.

The patients were divided into two groups according to the PA treatment method. Group 1 (n=40) was defined as patients treated with MRA, and group 2 (n=22) was defined as patients who underwent ADX. Groups were compared in terms of creatinine, eGFR, potassium, sodium, PAC, PRA, ARR, presence of hypertension, and hypokalemia. The percentage changes in creatinine, eGFR, sodium, and potassium were also compared between the groups. The patients were also compared separately according to the laboratory findings at baseline and the third month of the treatment in each group. A correlation analysis between the percentage of eGFR changes and the percentage of potassium change with clinical and laboratory parameters was also performed.

This study was approved by University of Health Sciences Turkey, İstanbul Training and Research Hospital Clinical Researches Ethics Committee with the decision number 2930 (date: 19.03.2021). Procedures were performed according to the ethical standards in the Helsinki Declaration.

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0. Categorical variables were defined as frequency and percentage rate, and numerical variables were determined as mean ± standard deviation. The Kolmogorov-Smirnov test assessed the normality of the distribution of the quantitative variables. The Student's t-test was performed for normally distributed numeric variables, and the Mann-Whitney U test was performed for non-normally distributed data for independent group comparison. Wilcoxon signed-rank test was used to evaluate paired differences in the levels before and after the treatment. Correlations were expressed by Pearson's correlation analysis or Spearman's correlation analysis when indicated. A p-value <0.05 was set as statistically significant.

RESULTS

Sixty-two patients (40 female/22 male) with PA were included in the study. The mean age of the whole study group was 54.0±9.9 years. The mean PAC and PRA levels in the whole study group were 40.6±36.6 ng/dL and 0.34±0.22 ng/mL/hour, respectively. Forthy-five patients had adrenal adenoma, and the mean adenoma size was 19.9±8.5 mm. All patients had hypertension at baseline, and 11 (50%) patients with adrenal adenoma had complete clinical success with hypertension without antihypertensive drugs after the treatment with ADX. A decrease in the number of drugs for hypertension was observed in the whole study group. Forthy-one patient had hypokalemia at baseline, and all of them resolved after the treatment with MRA or ADX. The patients were divided into groups according to the PA treatment method. Forty patients were followed up with MRA therapy (group 1), and 22 patients underwent ADX (group 2). PAC, ARR, and patients with hypokalemia at baseline were significantly higher in group 2 than in group 1 (p<0.001, p=0.006, and p=0.011; respectively). While potassium in the third month of the treatment was similar between the groups, potassium at baseline was significantly higher in group 1 than in group 2 (p<0.001). The eGFR levels at the baseline and at the third month of the treatment were similar between the groups. The percentage change in eGFR, sodium, and potassium in group 2 was significantly greater than that in group 1. (p=0.031, p=0.009 and p<0.001; respectively). The group comparison of the patient's clinical and laboratory findings treated with MRA or ADX is presented in Table 1.

The patients were also compared separately in each group for the patient laboratory findings at baseline and the third month of the treatment. While the pretreatment eGFR and sodium levels in both treatment groups were significantly higher than the levels in the third month of the treatment (p<0.001 and p<0.001; respectively), the pretreatment

Table 1. Comparison of the patient's clinical and laboratory findings treated with mineralocorticoid receptor antagonists or unilateral adrenalectomy

n=62	Group 1** (Treated with mineralocorticoid receptor antagonist) n=40	Group 2** (Treated with unilateral adrenalectomy) n=22	p
Female/male (n)	22/18	18/4	0.031
Age (years)	56.05±9.74	50.36±9.57	0.031
Patients with adenoma/without adenoma (n)	23/17	22/0	-
PAC (ng/dL)	26.89±15.25	66.67±49.77	<0.001
PRA (ng/mL/hour)	0.32±0.22	0.37±0.24	NS
ARR	122±109	262±242	0.006
Patients with hypokalemia (n, %)	22 (55)	19 (86)	0.011
Creatinine (mg/dL) (pretreatment)	0.74±0.23	0.77±0.22	NS
eGFR (mL/min) (pretreatment)	97.42±17.74	94.23±21.84	NS
Sodium (mEq/L) (pretreatment)	142.58±2.6	143.09±2.16	NS
Potassium (mmol/L) (pretreatment)	3.57±0.56	3.02±0.56	<0.001
Creatinine (mg/dL) (post-treatment)	0.90±0.27	0.98±0.28	NS
eGFR (mL/min) (post-treatment)	85.41±21.72	75.36±22.24	NS
Sodium (mEq/L) (post-treatment)	140.59±2.60	138.95±2.72	0.037
Potassium (mmol/L) (post-treatment)	4.50±0.47	4.72±0.55	NS
Percent change of the creatinine*	-23.18±28.17	-30.13±26.39	NS
Percent change of the eGFR*	11.59±19.54	20.12±14.85	0.031
Percent change of the sodium*	1.41±2.12	2.88±1.78	0.009
Percent change of the potassium*	-27.98±21.61	-60.44±31.03	<0.001

Data were given as mean ± standard deviation. PAC: Plasma aldosterone concentration, PRA: Plasma renin activity, ARR: Aldosterone/renin ratio, eGFR: Estimated glomerular filtration rate, NS: Non-significant, *[(the level at pretreatment-the level at the third month of treatment)/the level at pretreatment] × 100. **p<0.001 for all paired pre- and posttreatment comparisons in all groups (Wilcoxon test)

creatinine and potassium levels in both treatment groups were significantly lower than the levels in the third month of the treatment (p<0.001 and p<0.001; respectively).

The correlation analysis between the percentage of eGFR changes and the percentage of potassium change with clinical and laboratory parameters in the whole study group is presented in Table 2. Significant positive correlations were observed between the percentage of eGFR and the percentage of potassium change with ARR in the whole study group (r=0.403, p=0.002 and r=0.445, p<0.001; respectively).

DISCUSSION

We evaluated the effect of ADX and MRA treatment on clinical and biochemical outcomes in patients with PA in this study. While ARR and PAC were higher in patients with treated ADX than in the patients with MRA, potassium was lower in the patients with ADX. We also demonstrated that both specific treatments for PA (ADX or MRA) cause a decline in eGFR and sodium and an increase in potassium at the third month of the treatment. Furthermore, the percent change of eGFR, sodium, and potassium was more prominent in ADX than in the MRA treatment.

Table 2. Correlation between the percent change of eGFR and potassium with clinical and laboratory parameters in the whole study group

	Percent change of eGFR*		Percent change of potassium*	
n=62	**r**	**p**	**r**	**p**
Age (years)	0.140	0.282	0.100	0.442
Male gender	-0.157	0.227	-0.149	0.251
PAC (ng/dL)	0.344	0.007	0.490	<0.001
PRA (ng/mL/hour)	-0.100	0.452	-0.097	0.466
ARR	0.403	0.002	0.445	<0.001
Patients with hypokalemia at baseline	0.427	0.001	0.749	<0.001
Patients with adenoma	0.076	0.559	0.419	0.001

Data were given as mean ± standard deviation. PAC: Plasma aldosterone concentration, PRA: Plasma renin activity, ARR: Aldosterone/renin ratio, eGFR: Estimated glomerular filtration rate; *The percent change of eGFR and potassium between the level at pretreatment and the level at the third month of the treatment (mineralocorticoid receptor antagonists or unilateral adrenalectomy)

Previous studies have shown that the decline in eGFR following the treatment of the PA is primarily caused by the alleviation of hyperfiltration due to excessive mineralocorticoid effect (8-11). The decline in eGFR was also shown in both the treatment MRA and ADX in this study, but the percent change of eGFR was more prominent with the ADX than with the MRA treatment. Similar to our results, it was revealed that ADX lowered eGFR more prominent than that MRA (19). It was also shown in this study that ARR was higher, and potassium was lower in patients treated with ADX than in the patients treated with MRA. Thus, the more prominent decrease in eGFR in patients treated with ADX could also be explained by the presence of aldosterone-producing adenomas, more pronounced hypokalemia, and higher aldosterone levels. Aldosterone-induced glomerular hyperfiltration caused by higher aldosterone resolves after treatment and results in a more prominent eGFR decline. Aging causes significant changes in the structure and function of the glomerulus. Recent studies reported that older age was a risk factor for the significant decrease in eGFR in patients treated with ADX or MRA (19,20). Unlike these studies, we did not observe any association between age and eGFR decline in patients treated with ADX or MRA. However, a positive association between eGFR decline with ARR and PAC was also shown in this study. Consistent with our study, there were studies showing that the eGFR decline was greater if aldosterone was higher before treatment (7,20,21). Therefore, we speculate that baseline PAC and ARR may be more important than age for a decline in eGFR.

Hypertension may persist after the PA-specific treatment, and only approximately one-third of such patients normalize blood pressure without the use of any additional medical treatment for hypertension (22). While 50% of the patients treated with ADX did not need any antihypertensive drugs, a decrease in the number of drugs for hypertension was observed in all other patients. These findings suggest that the normalization of hypertension is more pronounced with ADX. It was also shown in another study that low serum potassium levels at baseline were an indicator of a decline in eGFR (7). A similar association was shown between the percentage change in eGFR and patients with hypokalemia in our study. We also evaluated the parameters related to the percent change of potassium with treatment in this study. It was shown that the percent change of potassium was associated with pretreatment PAC and adrenal adenoma existence. Furthermore, more hypokalemia was observed in patients treated with ADX, and post-treatment normokalemia was detected in all patients treated with both ADH and MRA.

There are some limitations to the present study. First, our study's retrospective and single-center design with a relatively small patient number may have affected the results of the study. Secondly, patients treated ADX had a more pretreatment biochemical severity of PA than those treated with MRA, which may impact our clinical results.

CONCLUSION

ADX and MRA treatments could provide the amelioration of renal function, resolve hypertension and normalize potassium levels in patients with PA. Aldosterone-induced glomerular hyperfiltration in PA resolves after both ADX and MRA treatments and results in a more prominent eGFR decline, especially in patients treated with ADX. These findings suggest that all patients should be carefully evaluated for the feasibility of ADX therapy. Moreover, MRA could be considered as an effective treatment option, especially for patients not candidates for ADX. Therefore,

physicians should be aware of evaluating the renal function after the treatment because pretreatment eGFR alone may not be a good predictor of renal function. The early detection of renal disease after the treatment is important to prevent adverse outcomes.

ETHICS

Ethics Committee Approval: This study was approved by University of Health Sciences Turkey, İstanbul Training and Research Hospital Clinical Researches Ethics Committee with the decision number 2930 (date: 19.03.2021). Procedures were performed according to the ethical standards in the Helsinki Declaration.

Informed Consent: Retrospective study.

Authorship Contributions

Concept: S.T., H.P., Design: H.P., Data Collection or Processing: S.T., H.P., Analysis or Interpretation: S.T., H.P., Literature Search: S.T., H.P., Writing: S.T., H.P.

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