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Original Article

EFFECT OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN-II RECEPTOR BLOCKERS ON PROTEINURIA OF HYPERTENSIVE PATIENTS IN STANDARD CARE PRACTICE

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ABSTRACT

Objective: This study investigated the effect of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin-ii receptor blockers (ARBs) on protein creatinine index (PCI) of patients with hypertension in a standard care practice.

Methods: This retrospective study was carried out in a tertiary hospital. Hypertensive patients were randomly selected and screened based on inclusion and exclusion criteria. PCI values were obtained from the patient's medical record.

Results: No significant differences were observed in the percentage of patients with proteinuria (PCI ≥20 mg/mmol creatinine) at pre-and post-treatment among the patients treated with ACEI, ARB or non-ACEI/ARB. Patients treated with ACEI (-10 mg/mmol creatinine; IQR-37.5-+10; p<0.046) and ARB (-10 mg/mmol creatinine; IQR-30-+10; p<0.048) showed significant reduction in PCI values at post-treatment compared to the non-ACEI/ARB group (+5 mg/mmol creatinine; IQR 0-+32.5).

Conclusion: Our findings demonstrated that standard care practice, the therapy of ACEI and ARB did not sufficiently reduce the number of patients with proteinuria but could reduce progression of the proteinuria.

Keywords: Proteinuria, Protein creatinine index, ACEI; ARB.

INTRODUCTION

A clinically significant presence of protein in the urine occurs due to the ineffectiveness of renal tubular reabsorption of albumin and small-sized protein molecules [1]. Proteinuria refers to increased urinary excretion of albumin, other specific proteins, or total protein [2]. The severity of proteinuria is usually described as the amount of albumin present in the urine for example microalbuminuria or macro albuminuria, or as an index of protein to creatinine ratio (PCI).

Proteinuria is an early sign and can be monitored for the progression of renal diseases [3]. Depending on age and ethnicity, 7 to 40% of individuals with hypertension have proteinuria in a form of microalbuminuria [4]. Albuminuria is a well-known predictor of poor renal outcomes in patients with diabetes mellitus (DM) and hypertension [5]. The severity of proteinuria may also be a significant predictor of cardiovascular events in a population with DM nephropathy and hypertension [6, 7].

Increased risk of cardiovascular events may be associated with increased levels of inflammatory markers or endothelial dysfunction which are commonly detected with high levels of proteinuria [8]. Improved epithelial function due to early blockade of the renin angiotensin aldosterone system (RAAS) may explain the mechanism of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) in reducing the risk for cardiovascular events. ACEIs and ARBs are effective in the treatment of hypertension. Well-designed clinical trials have demonstrated that both groups of agents are also able to preserve renal function in chronic kidney disease (CKD) and reduce proteinuria [9-14]. Nevertheless, the data on the effect of these agents on proteinuria in the standard care practice is limited. This study aimed to determine the changes of PCI in patients treated with ACEIs, ARBs or other antihypertensive agents in a routine standard care practice.

MATERIALS AND METHODS

This retrospective study was approved by the University Kebangsaan Malaysia Research Ethic Committee (UKM 1.5.3.5/244/NF-005-2011). Medical records of patients who received hypertensive therapy between June 2008 and June 2010 were reviewed and the data was analysed. The patients were not specifically recruited for any other clinical trial and the data in the medical records were from their routine scheduled visits to the medical clinic.

A total of 1096 patients with hypertension were randomly identified from the Computerised Pharmacy Management System using the random number generator. All of these patients were screened according to the inclusion and exclusion criteria. Patients included in the analysis had at least 2 PCI readings; pre treatment PCI (pre-PCI) which was the reading of PCI within one month before the initiation of antihypertensive therapy and post treatment PCI (post-PCI) which was the reading of PCI after at least 3 mo on antihypertensive therapy. Average pre-or post-PCI reading was used in patients with more than one PCI reading. Patients with end stage renal failure and immune related nephropathy such as systemic lupus erythematosus diseases were excluded from the study. Based on these inclusion and exclusion criteria, 51 patients were identified as suitable subjects (ACEI group represented by 28 patients, ARBs group represented by 15 patients and non-ACEI/ARB group represented by 8 patients). Major exclusion factor for the subjects was insufficient PCI data.

The PCI readings were supplied by the Hospital's Clinical Biochemistry Laboratory as part of the standard medical care monitoring parameters. PCI of less than 20 mg/mmol creatinine was classified as normo proteinuria and PCI of 20 mg/mmol creatinine and above was classified as proteinuria. Change in PCI (dPCI) was the difference between post-PCI and pre-PCI. The PCI was evaluated regardless of the dosage regimen and specific antihypertensive agent in the group. Patients who received ACEI or ARB were also allowed to receive other antihypertensive agents from other pharmacological classes. The direction of changes in PCI after the treatment was marked with the sign of negative (-) and positive (+) for reduction and increment in PCI, respectively. Parametric statistical tests were employed for continuous data that was normally distributed. Non-parametric statistical tests were employed for data that was nominal or ordinal in nature and continuous data with skewed distribution. Results are presented as

either number of items (n) with the percentage (%), mean with standard deviation (SD) or median with inter-quartile range (IQR).

RESULTS

The baseline characteristics of the patients are presented in table 1. None of the baseline characteristics were significantly different among the three treatment groups except for the systolic and diastolic blood pressures between the ACEI (median 151/83 mmHg) or ARB (median 150/80 mmHg) treatment groups and the non-ACEI/ARB (median 124/70 mmHg) treatment group ($p<0.05$). The ACEI group included patients treated with captopril (n = 1), enalapril (n = 11), imadapril (n = 3), perindopril (n = 10) and ramipril (n = 3).

The ARB group included patients treated with irbesartan (n = 3), losartan (n = 6), telmisartan (n = 4) and valsartan (n = 2). The pre-PCI readings among the treatment groups also showed no significant difference ($p=0.123$).

Table 1: The characteristics of patients at baseline before antihypertensive therapy

Characteristics	Treatment group		
	ACEI	ARB	Non-ACEI/ARB
No. of patients	28	15	8
Age, mean (SD) years	63.0 (7.7)	62.8 (5.9)	68.8 (8.3)
Body Mass Index, mean(SD) kg/m^2	30.1 (5.2)	31.7 (5.7)	28.7 (4.8)
Gender, n (%)			
Male	17 (60.7)	10 (66.7)	6 (75.0)
Female	11 (39.3)	5 (33.3)	2 (25.0)
Race, n (%)			
Malay	14 (50.0)	10 (66.7)	6 (75.0)
Chinese	12 (42.8)	4 (26.7)	2 (25.0)
Indian	1 (3.6)	1 (3.6)	0 (0.0)
Others	1 (3.6)	0 (0.0)	0 (0.0)
Systolic BP, median (IQR) mmHg*	151 (137-160)	150 (133-160)	124 (120-133)
Diastolic BP, median (IQR) mmHg*	83 (77-90)	80 (71-82)	70 (61-73)
Creatinine clearance, median (IQR) ml/min	44 (38-67)	40 (32-62)	32 (24-42)
Protein Creatinine Index (pre-PCI), median (IQR)	50 (20-220)	50 (30-150)	15 (10-65)
Co-morbidities, no. of patients			
Hypertension	28	15	8
Type II diabetes mellitus	25	13	8
Ischemic heart disease	8	4	3
Chronic kidney disease	22	14	8
Hyperlipidemia	26	12	8
Congestive heart failure	1	0	1
Cerebrovascular disease	3	0	3
Concurrent medication, no. of patients			
Diuretics	16	12	6
Beta-blockers	18	12	6
Calcium channel blockers	23	13	6
Alpha-blockers	4	1	3
Antiplatelets	19	10	6
Insulin	20	12	5
Statins	28	14	7
Fibrates	8	10	3

*One-way ANOVA with post hoc; Significant for ACEI versus non-ACEI/ARB or ARB versus non-ACEI/ARB; $p<0.05$., ACEI, angiotensin converting enzyme; ARB, angiotensin-II receptor blocker; SD, standard deviation; IQR = inter-quartile range.

Based on the PCI 20 mg/mmol creatinine value as a cutting point for category of proteinuria, none of the treatment groups has shown significant changes between the pre-and post-proteinuria (ACEI group, $p=0.956$; ARB group, $p=0.585$; non-ACEI/ARB group, $p=0.144$). The median duration between the pre-PCI and post-PCI readings was 16 mo (IQR 9 to 21 mo). The dPCI before and after the treatment are presented in fig. 1. The dPCI for the ACEI group was-10 mg/mmol creatinine (IQR-37.5 to+10), for the ARB group was-10 mg/mmol creatinine (IQR-30 to+10) and for the non-ACEI/ARB group was+5 mg/mmol creatinine (IQR 0 to+32.5). No significant different in dPCI was demonstrated between the ACEI and ARB groups ($p=0.766$). Marginal differences in dPCI were demonstrated between ACEI and non-ACEI/ARB groups ($p<0.046$), and between ARB and non-ACEI/ARB groups ($p<0.048$).

DISCUSSION

Several methods to describe proteinuria have been established [2]. Among others, PCI and albumin creatinine ratio are consideration as quantitative measures of proteinuria. These tests should be done within 3 mo of a positive dipstick test. The advantage of using PCI include corrected to the variation of urine concentration due to abnormal hydration and inconsistent protein excretion rate at different times during the day [2]. Accordingly, in this study, the PCI was employed as the quantitative measure of proteinuria before and after the treatment.

Protein molecules which pass through the glomerular loops into the urine will be reabsorbed by active transport mechanisms in the proximal tubule. This reabsorption process has a limited capacity. If the amount of proteins exceeds this capacity, a pathologic proteinuria will develop. Conditions such as hypertension and hyperglycemia state may exacerbate the severity of proteinuria [15]. Other than being a marker for the risk of renal disease, protein in the urine also contributes to kidney damage. Proteins are toxic to the renal tubular cells and cause tubulointerstitial inflammation and scarring [16].

Several clinical trials have demonstrated the effects of ACEIs and ARBs on reducing proteinuria [9-14]. Nevertheless, in the current study, the effect of both agents in reducing proteinuria status was not established. Based on the category of proteinuria with a cut-off

point of 20 mg/mmol creatinine, all treatment groups did not show any significant improvement in the number of patients without proteinuria.

However, this may not necessarily indicate that ACEI or ARB do not play an important role in the management of hypertensive patients with proteinuria. The findings may however indicate that both groups of agents have the capacity to prevent the progression of proteinuria.

The risk to develop end-stage renal failure may be reduced if the overt proteinuria progression can be stopped [17].

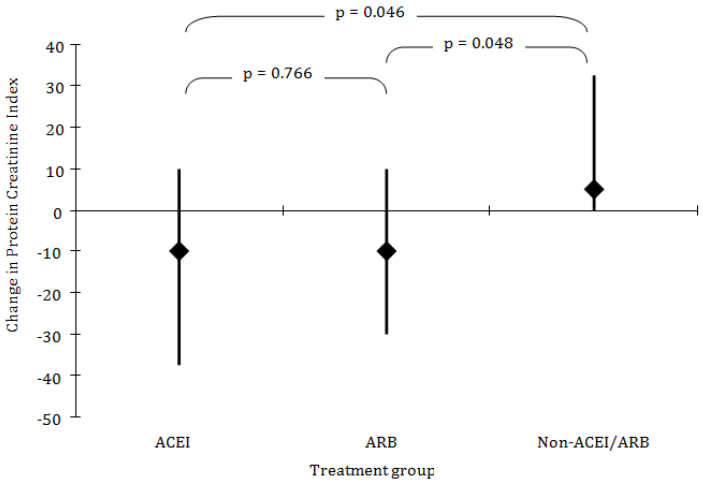

Fig. 1: Changes in protein creatinine index at post treatment among antihypertensive treatment groups. ◆ Shape represents the median; horizontal bold line represents the inter-quartile range; ACEI, angiotensin converting enzyme; ARB, angiotensin-II receptor blocker

It is imperative to be aware that the evaluation of proteinuria based on a cut-off point may conceal the moderate yet beneficial effect of ACEIs and ARBs. Based on the PCI readings, there was a significant reduction in the amount of protein in the urine of patients treated with ACEI or ARB as compared to patients treated with non-ACEI/ARB antihypertensive agents. This supports the ability of ACEI and ARB in preventing overt progression of proteinuria. The effects demonstrated in previously published well-designed clinical trial were evidently replicated in the current study. In patients with hypertension and hyperglycemia, the activation of RAAS can worsen the glomerulus capillary hypertension [15]. This condition increases glomerulus permeability and protein filtration to the urine. ACEIs and ARBs reduce the intra glomerular pressure by inhibiting the angiotensin II-mediated efferent arteriolar vasoconstriction. This may explains the greater reduction in proteinuria by ACEIs and ARBs. The specific renoprotective effect of the ACEIs and ARBs may be more pronounced than the antihypertensive effects especially in patient with diabetic nephropathy [18]. The control of hypertension in this population is usually achieved with combination therapy with other group antihypertensive agents such as calcium channel blockers and diuretics. Baseline blood pressure was significantly lower in the non-ACEI/ARB group compared to ACEI or ARB groups. Based on this baseline blood pressure, it was not expected that the non-ACEI/ARB group will progress to the worsening of protenuria status. However, our findings contradicted with our expectation. This grossly supported the advantages of employing ACEI or ARB in hypertension management.

The current study findings have highlighted the important of ACEI and ARB in the management of hypertension with proteinuria, nevertheless the findings should be deduced with caution due to several limitations. The limited sample size, amount of medication dose, other medications that may affect the protein levels and intra-individual variability in the urine protein levels may have influenced indirectly the findings. Number of patients on ACEI or ARB therapy at screening was large, however, the monitoring of pre-and post-treatment urine protein was not routinely carried out for majority of this patients in the standard care practice. Thus, this affected the sample size.

In conclusion, although ACEIs and ARBs did not improve the number of patients without proteinuria, the effects of both agents in preventing progression of overt proteinuria have been demonstrated in the standard care practice.

CONFLICT OF INTERESTS

Declared none

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