Effectiveness of Antihypertensive Drugs in Hypertensive Patients With End Stage Renal Failure

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SUMMARY

Hypertension has been identified as one of the causes for end stage renal failure (ESRF) and is likely to worsen kidney function. This retrospective study was carried out at a tertiary hospital in Malaysia with the objective of determining the effectiveness of combination antihypertensive drugs in hypertensive patients with ESRF admitted between 2006 and 2008. Patients with incomplete data and who were on monotherapy were excluded from this study. Although six different combinations gave significant reductions in systolic blood pressure (SBP) (13.38 ± 9.11 mmHg, p<0.05) and diastolic blood pressure (DBP) (6.03 ± 11.39 mmHg, p<0.05), 69.16% patients did not achieve target blood pressure (BP) (≤ 130/80 mmHg). Combination of beta blocker (BB) with calcium channel blocker (CCB) was the most commonly used. The CCB-diuretic regimen achieved highest percentage of BP control compared to others (40%). Comparison of blood pressure reduction between different combinations of antihypertensive drugs were not significant (p>0.05) except for CCB-diuretics and BB-CCB-alpha blocker. The findings suggested better BP control with CCB-diuretic relative to other combinations used.

KEY WORDS:
Antihypertensive drugs; efficacy; end stage renal failure; hypertension; combination therapy

INTRODUCTION

Hypertension, is simply defined as continuous increase in systolic blood pressure (SBP) exceeding 140 mmHg and/or diastolic blood pressure (DBP) more than 90 mmHg [1]. In Malaysia, the prevalence of hypertension in adults increased in the last 10 years. It is estimated about 4.8 million Malaysians are suffering from hypertension [2].

End stage renal failure (ESRF) is defined as deterioration of kidney function as glomerular filtration rate (GFR) declines to less than 15 ml/min/1.73 m^2. According to National Kidney and Urologic Disease Information Clearinghouse (NKUDIC) [3], there were 506,256 United States people who were diagnosed with end stage renal failure (ESRF). From that amount, 122,339 cases were caused by uncontrolled hypertension. It was identified as the second major cause of ESRF after diabetes mellitus. Good blood pressure (BP) control can help retard or delay severe complications of this disease.

Classes of antihypertensive drugs include the calcium channel blockers (CCB), beta blockers (BB), alpha blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptors blockers (ARB), diuretics, centrally acting agents and direct vasodilators [1]. According to Wenzel *et al* [4], treatment with one antihypertensive drug is not an effective strategy. Combination therapy with different classes of antihypertensive drugs is required. The advantages of combination therapy for hypertension include better blood pressure control through synergistic effect, incidence of side effects and increased economy and efficiency outcome [5].

Most hypertensive patients without comorbidities will require at least two antihypertensive drugs to achieve target goal, while for hypertensive patients with concomitant diabetes or chronic kidney disease, three or more antihypertensive drugs must be employed early in order to achieve the blood pressure goal below 130/80 mmHg. For the latter group of patients, combination therapy can be started when blood pressure exceeds 20/10 mmHg from the ideal BP goal [6].

According to the Third NHMS [2], 74% of Malaysians who received antihypertensive treatment did not achieve targeted blood pressure. Only 11% of hypertensive patients with ESRF achieved targeted blood pressure [7]. 65% of physicians tried to control blood pressure with only one drug. However, most of the patients subsequently needed combination therapy [6]. A trial that had been carried out by Julius S *et al* [8] showed that 85% of patients received at least two drugs to achieve blood pressure less than 140/95 mmHg. The study encouraged physician to increase doses, add another classes of medicines in order to obtain goal blood pressure.

A guideline is the result of a comprehensive systemic review of clinical trial data and concludes the initial therapy for particular diseases to guarantee the most effective therapy is being started [9]. In Malaysia, Clinical Practice Guidelines Management of Hypertension 2008 is used as guidance to produce best response in controlling blood pressure [1].

The aims of this study were to determine the effectiveness of combination therapy in reducing blood pressure for hypertensive patients with ESRF, evaluate combination hypertensive treatment for patients in achieving targeted blood pressure, determine the effect of hypertensive treatment on the creatinine clearance and study the relationship between the systolic and diastolic blood pressure reduction.

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MATERIALS AND METHODS

Study Design

The study was conducted retrospectively in a local tertiary hospital. The name and registration number of hypertension patients with ESRF hospitalized between 2006 to 2008 were obtained from the case mix unit and medical records from Record Unit over a 4 month period. Meanwhile, hypertensive patients with ESRF who did not have complete data, had not been prescribed with antihypertensive drugs and had only been treated with monotherapy were excluded from the study. The data from medical records were collected by using a data collection form which consisted of demographic data (name, registration number, age, gender, race and weight), past medication history, current medical problems, drug therapy, laboratory investigations and vital signs including blood pressure. Readings were taken at the time of taking antihypertensive drugs and 2 to 3 hours after.

Sampling Method

A list of 139 patients was provided by the case mix unit. However, only 107 patients fulfilled the inclusion criteria of this study. The sampling method that was used was universal sampling since there were not many hypertensive patients with ESRF admitted within the study period.

Definition

Some terms used are defined as the following. Hypertension is systolic blood pressure of > 140 mmHg or diastolic blood pressure of > 90mmHg, or requiring the use of antihypertensive drug whereas ESRF is defined as creatinine clearance less than 15 mL/min. Anemia is defined as hemoglobin value less than 13.5 g/dL for male and 12.0 g/dL for female, while hypocalcaemia is defined as calcium level less than 2.14 mmol/L. Hyperphosphatemia is defined as phosphate level higher than 1.36 mmol/L [10, 11].

Data analysis and presentation

The collected data were analysed by using Statistical Package for Social Sciences (SPSS) version 18.0. The demographic data, causes of ESRF, proportion of blood pressure control, incidence of anemia, hypocalcaemia and hyperphosphatemia were analysed descriptively. By using Kolmogrov Smirnov and Shapiro Wilk Test of Normality, normality of the data had been determined. A two-tailed paired t test with alpha level of 0.05 was applied to compare the blood pressure (systolic and diastolic blood pressure) before and after taking the hypertensive drugs. Apart from that, paired sample t-test was also used to compare the mean of creatinine clearance between the day of admission and the day of discharge. One-Way ANOVA was used to compare the mean difference in blood pressure reduction (systolic and diastolic blood pressure) between different combinations of antihypertensive drugs. Spearman's Rho correlation test was employed to determine the relationship between the systolic and diastolic blood pressure reduction.

Finally, the collected and analysed data were presented using tables, charts and graphs by using Microsoft Office ExcelTM. Presentation of data was done based on the demographic data and objectives of the research.

RESULTS

107 patients were included in this study. Their demographic data were summarised in Table I. For gender distribution, there were more female patients (n=61, 57%) than male patients (n=46, 43%). Most of the patients that were involved in this study were Malay (n=52, 48.6%), followed by Chinese (n=47, 43.9%), Indians (n=6, 5.6 %) and others (n=2, 1.9%). The mean age range was 59 ± 12 years old. There were 65.4% of elderly patients who were at least 65 years old. The remaining 34.6% of patients were below 65 years old.

ESRF was mainly caused by hypertension (n=39, 36.4%), followed by diabetes mellitus (n=34, 31.8%), chronic kidney disease (n=11, 10.3%) and others (n=23, 21.5%) which included unknown cause, drugs and age of patients. The results are shown in Table II.

There were six different combinations of antihypertensive drugs that had been used in controlling blood pressure of hypertensive patients with ESRF as shown in Table III. Most of the patients were given BB with CCB (n=33, 30.8%) and both combinations of BB, CCB with alpha blocker and BB, CCB with ACE inhibitor were the least combinations of antihypertensive drugs used (n=11, 10.3%).

Figure 1 illustrates that only 30.84% (n=33) of patients had achieved goal blood pressure (≤130/80 mmHg) and the remaining 69.16% or 74 patients did not achieve the target.

From Figure 2, it could be noted that 80.0% of the patients on combination of CCB with alpha blockers did not reach targeted blood pressure whereas 40.0% of patients treated with combination of CCB with diuretic had achieved targeted blood pressure.

Table IV shows the mean difference of SBP and DBP before and after taking antihypertensive drugs. On average, mean difference of SBP before and after taking antihypertensive drugs were statistically significant (13.38 ± 9.11 mmHg, $p<0.05$) with combination of CCB and alpha blocker, showing the largest SBP reduction (14.98 ± 11.38 mmHg, $p<0.05$).

Overall, patients' DBP showed a significant decrease after taking antihypertensive drugs with $p<0.05$. The mean difference of DBP was 6.03 ±11.39 mmHg. Results revealed that the greatest mean difference of DBP was observed in patients taking BB with CCB and alpha blockers (10.99 ± 18.65 mmHg, $p<0.05$). However, mean difference of DBP before and after taking combination of CCB and diuretics was statistically non significant (-0.02 ± 14.73 mmHg, $p>0.05$).

Table V compares blood pressure reduction between different types of antihypertensive drugs combinations. For comparison of DBP reduction between different types of combinations, a non significant mean difference was noted except comparison of DBP between the combination of CCB and diuretics with the combination of BB, CCB and alpha blocker. The mean difference between these two combinations was -11.01± 3.68 mmHg with $p<0.05$. The mean difference of SBP reduction between different types of combination did not show statistical significance ($p>0.05$).

Table I: Gender, race and age distribution of hypertension patients with ESRF

	Number of Patients (n=107)	Percentage (%)
Gender		
Male	46	43.0
Female	61	57.0
Race		
Malay	52	48.6
Chinese	47	43.9
Indian	6	5.6
Other	2	1.9
Age, mean ± standard deviation	59 ± 12	
< 65 years old	70	65.4
≥ 65 years old	37	34.6

Table II: Identified Risk factors of ESRF

Causes	Number of Patients (n=107)	Percentage (%)
Hypertension	39	36.4
Diabetes Mellitus	34	31.8
Chronic Kidney Disease	11	10.3
Others	23	21.5

Table III: Combinations of antihypertensive drugs used in hypertensive patients with ESRF

Combinations of Antihypertensive Drugs	Number of Patients (n=107)	Percentage (%)
BB + CCB	33	30.8
CCB + α–Blockers	15	14.0
CCB + loop diuretic	20	18.7
BB + CCB + α-Blockers	17	15.9
BB + CCB + ACEI	11	10.3
BB + CCB + loop diuretic	11	10.3

Table IV: Mean difference of blood pressure before and after taking antihypertensive drugs

Blood pressure	Mean difference ± standard deviation (mmHg)	P value (%)
Systolic	13.38 ± 9.11	0.000*
BB + CCB	13.33 ± 8.73	0.000*
CCB + α-Blockers	14.98 ± 11.38	0.000*
CCB + Diuretic	10.97± 7.49	0.000*
BB + CCB + α-Blockers	14.89 ± 11.39	0.000*
BB + CCB + ACEI	14.58 ± 9.48	0.000*
BB + CCB + Diuretic	12.18 ± 5.25	0.000*
Diastolic	6.03 ± 11.39	0.000*
BB + CCB	6.19 ± 6.48	0.000*
CCB + α-Blockers	7.57 ± 7.79	0.002*
CCB + Diuretic	-0.02 ± 14.73	0.996
BB + CCB + α-Blockers	10.99 ± 18.65	0.027*
BB + CCB + ACEI	6.45 ± 7.06	0.013*
BB + CCB + Diuretic	6.34 ± 4.18	0.001*

* The mean difference is significant at the 0.05 level

Table V: Comparison of blood pressure reduction between different combinations of antihypertensive drugs

Combination of antihypertensive drugs (I)	Combinations of antihypertensive drugs (J)	Mean difference (I-J)	P value
Systolic blood pressure			
BB + CCB	CCB + α-Blockers	-1.65 ± 2.87	0.992
	CCB + Diuretic	2.36 ± 2.61	0.945
	BB + CCB + α-Blockers	-1.56 ± 2.75	0.993
	BB + CCB + ACEI	-1.25 ± 3.21	0.999
	BB + CCB + Diuretic	1.14 ± 3.21	0.999
CCB + α-Blockers	CCB + Diuretic	4.01 ± 3.15	0.798
	BB + CCB + α-Blockers	0.09 ± 3.26	1.000
	BB + CCB + ACEI	0.40 ± 3.66	1.000
	BB + CCB + Diuretic	2.79 ± 3.66	0.973
CCB + Diuretic	BB + CCB + α-Blockers	-3.92 ± 3.04	0.790
	BB + CCB + ACEI	-3.61 ± 3.46	0.901
	BB + CCB + Diuretic	-1.22 ± 3.46	0.999
BB + CCB + α-Blockers	BB + CCB + ACEI	0.31 ± 3.56	1.000
	BB + CCB + Diuretic	2.70 ± 3.56	0.974
BB + CCB + ACEI	BB + CCB + Diuretic	2.40 ± 3.93	0.990
Diastolic blood pressure			
BB + CCB	CCB + ALPHA	-1.37 ± 3.47	0.999
	CCB + Diuretic	6.21 ± 3.16	0.369
	BB + CCB + α-Blockers	-4.80 ± 3.33	0.702
	BB + CCB + ACEI	-0.25 ± 3.88	1.000
	BB + CCB + Diuretic	-0.15 ± 3.88	1.000
CCB + α-Blockers	CCB + Diuretics	7.58 ± 3.81	0.355
	BB + CCB + α-Blockers	-3.43 ± 3.95	0.953
	BB + CCB + ACEI	1.12 ± 4.43	1.000
	BB + CCB + Diuretic	1.22 ± 4.43	1.000
CCB + Diuretic	BB + CCB + α-Blockers	-11.01 ± 3.68	0.040*
	BB + CCB + ACEI	-6.46 ± 4.19	0.637
	BB + CCB + Diuretic	-6.36 ± 4.19	0.653
BB + CCB + α-Blockers	BB + CCB + ACEI	4.54 ± 4.31	0.898
	BB + CCB + Diuretic	4.65 ± 4.31	0.889
BB + CCB + ACEI	BB + CCB + Diuretic	0.11 ± 4.75	1.000

* The mean difference is significant at the 0.05 level

Table VI: Spearman's rho correlation between systolic and diastolic blood pressure reduction

Factor		Systolic blood pressure reduction	Diastolic blood pressure reduction
Systolic blood pressure reduction	Correlation Coefficient (R)	1	0.353**
	Sig. (2-tailed)		0.000*
	N	107	107

* Correlation is significant at the 0.01 level
** R 0.2-0.5 = medium correlation

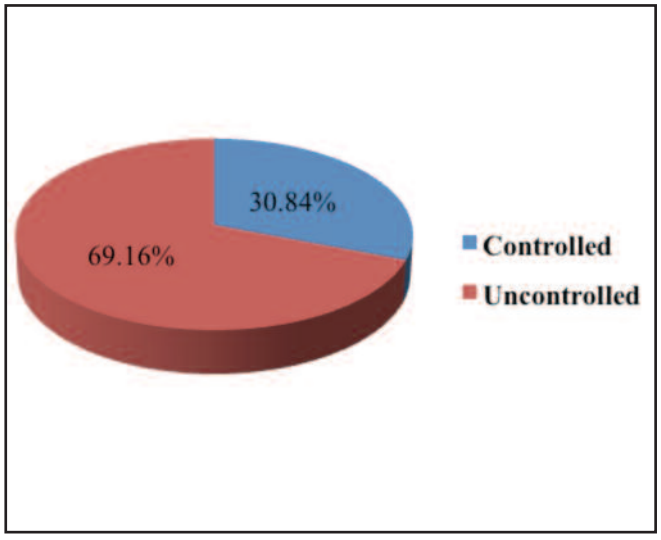
Table VII: Mean difference of creatinine clearance at the day of admission and at the day of discharge

Creatinine clearance	Mean difference ± standard deviation (ml/min)	P value
At the day of discharge – At the day of admission	1.16 ± 4.64	0.013*

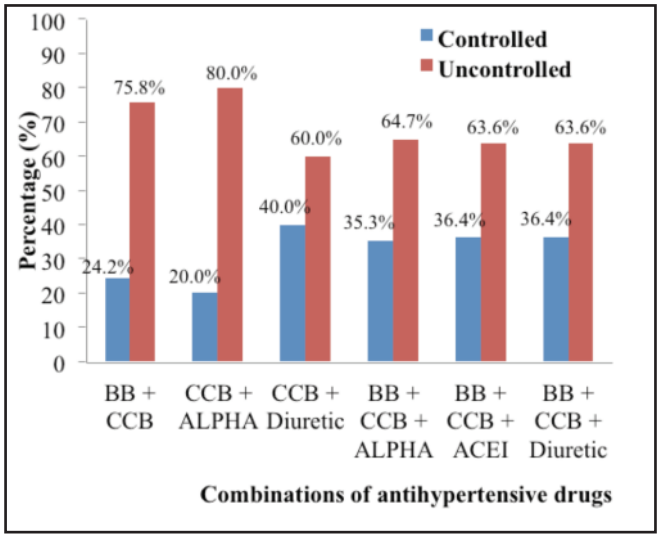
* The mean difference is significant at the 0.05 level

Table VIII: Number of patients having anemia, hypocalcaemia and hyperphosphatemia

	Number of Patients (n=107)	Percentage (%)
Anemia		
Normal hemoglobin level	11	10.3
Low hemoglobin level	96	89.7
Calcium level		
Normal	46	43.0
Low	49	45.8
High	2	1.9
Missing value / do not take the calcium level	10	9.3
Phosphate level		
Normal	32	29.9
High	61	57.0
Low	3	2.8
Missing value / do not take the phosphate level	11	10.3



*Note: Controlled blood pressure: ≤ 130/80 mmHg
Fig. 1: Proportion of blood pressure control for hypertension patients with ESRF.



*Note: Controlled blood pressure: ≤ 130/80 mmHg
Fig. 2: Percentage of blood pressure control based on different combinations of antihypertensive drugs.

For correlation between the SBP reduction and DBP reduction, Spearman's Rho correlation test indicated the presence of significant positive relationship between the SBP reduction and DBP reduction ($r(105)= 0.353$, $p<0.05$). A medium correlation was observed ($r=0.353$) (Table VI).

Table VII shows the mean difference of creatinine clearance of patients during admission and discharge. The creatinine clearance of patients during discharge was higher than creatinine clearance during the admission. The mean difference between creatinine clearance of patients during admission and at discharge (1.16 ± 4.74 ml/min) was statistically significant ($p<0.05$).

Number of patients having anemia, hypocalcaemia and hyperphoshatemia are shown in Table VIII. Most of the patients (n=96, 89.7%) developed anemia during hospitalization. 49 patients (45.8%) had low calcium level whereas patients with high phosphate level (n=61, 57%) outnumbered those with normal phosphate level (n=32, 29.9%).

DISCUSSION

According to Manley *et al.* [12], diabetes mellitus was the main cause of ESRF (47.8%) and it was followed by hypertension (22.4%). In 2006, Lim Y.N and Lim T.O also reported that hypertension was the second most common primary cause (7%) of ESRF in Malaysia in 2005, amounting to 185 cases for that year. However from this study, the incidences of ESRF were mainly caused by hypertension (n=39, 36.4%) and followed by diabetes mellitus (n=34, 31.8%). There were no significant difference in the number of patients with ESRF caused by hypertension and those caused by diabetes mellitus. The different findings may be due to the size of this study sample not being large enough to represent the real situation. However, it showed that patients with hypertension or diabetes mellitus had higher chance of developing ESRF compared to others. According to the National Kidney Foundation [13], high blood pressure can lead to worsening of kidney function as it can damage blood vessels throughout the body and thus reduce blood supply to important organs such as the kidneys. Thus it is important that blood pressure for hypertensive patients be monitored and controlled to maintain below 130/80 mmHg in order to prevent the progression of kidney deterioration.

Controlling the blood pressure is a commendable goal of antihypertensive therapy. In this hospital, most of the hypertensive patients with ESRF were treated with combination therapy. Ridao *et al.* [14] revealed that in 95% of renal patients, antihypertensive drugs were required and usually consisted of two or more drugs. The data showed that an average 1.9 drugs were necessary to control blood pressure at <125/75 mmHg and 1.5 for a blood pressure <140/90 mmHg. However, 65% physicians continued to prescribe monotherapy for this group of patients [6]. Basically, six different types of antihypertensive drugs combinations had been chosen to treat hypertensive patient with ESRF in this institution. The combination of BB and CCB was the most common combination that had been prescribed for the patients (n=33, 30.8%). Hoffmann [15] compared between metoprolol and felodipine combination tablets with each component alone as antihypertensive therapy. A significant greater reduction in mean SBP and DBP (28/18 mmHg) with combination therapy was evident compared to either felodipine (18/12 mmHg) or metoprolol (19/12 mmHg) alone. Bakris *et al.* [16] recommended an ACE inhibitor or ARB as first line therapy for the management of hypertensive patient with ESRF. The addition of thiazide diuretic will often be required. Furthermore, if patients' serum creatinine is more than 200µmol/L, thiazide diuretic may not be effective as an antihypertensive and therefore loop diuretic is preferred[1]. In this study, only 11 patients were given ACE inhibitor or ARB along with other antihypertensive drugs. It showed that the management of hypertension patients with ESRF in this institution is not consistent with the recommendations by Bakris *et al.* [17]. Concerns on deterioration of kidney function may explain why ACE inhibitor was not commonly prescribed. Boiskin M.M. (18) found that the ACE inhibitor had higher chance to induce renal failure in older patients. However, renal insufficiency should not be a contraindication to start ACE inhibitor or ARB therapy, nor should it be a reason for discontinuing therapy as claimed by Abdul Rashid *et al.* [1]. In fact, Brenner *et al.* [19] in RENAAL study demonstrated ARB could decrease the incidence of doubling serum creatinine concentration by 25% (p=0.006) as well as ESRF by 28% (p=0.002). Moreover, Lewis *et al.* [20] in the IDNT study found doubling of serum creatinine occured less in ARB-treated patients (16.9%) compared to CCB-treated patients (25.4%) and the rate with ARB was 37% slower than CCB ($p<0.01$). ACE inhibitors was more effective in slowing the decline of GFR compared to beta blockers or dihydropyridine CCB as shown by Agoda *et al.* [21] in the AASK study. Thus it should not be a problem to start treatment with ACE inhibitors or ARB but serum creatinine level should be checked within the first two weeks of initiation of therapy. If there is a persistent rise of serum creatinine of ≥30% from the baseline within two months, ACE inhibitor or ARB should be stopped [1].

Hypertension is a risk factor in the progression of chronic renal failure [22]. A strict control of blood pressure is necessary in preventing or delaying the decrease in renal function as well as reducing the risk of getting cardiovascular disease [14]. Wenzel [4] recommended lowering blood pressure to at least 140/90 mmHg in patients with uncomplicated hypertension while 130/80 mmHg for patients with diabetes or chronic kidney disease. From the study, it showed that only 30.84% patients' achieved goal blood pressure (≤ 130/80 mmHg). Neutel [23] also found that in fact, less than 50% of treated hypertensive patients had reached the targeted blood pressure. There are several possible reasons as to why blood pressure was difficult to be controlled. Firstly, poor adherence to treatment suggested by guidelines may be one of the main causes. However, recommendations from the guideline may not be appropriate for all patients in a particular category [24]. Secondly, renal function of the patients had already been severely deteriorated , thus pharmacokinetics of the antihypertensive drugs may be altered. Besides that, peripheral resistance, volume overload, increased cardiac output and arterial stiffness may have contributed to the uncontrolled blood pressure in patients with ESRF [25]. Less than 25% of patients in each group of BB with CCB and

combination of CCB with alpha blocker achieved targeted blood pressure. This may be related to high blood pressure during admission, that was 170.97/85.45 ± 23.98/15.81 mmHg and 175.93/88.73 ± 15.39/16.82 mmHg respectively. Although these combinations gave significant blood pressure reduction, they did not give optimal outcomes. The CCB with diuretic group achieved the highest number of patients with controlled blood pressure (40%). This may be related to the patients' relatively low blood pressure upon admission (155.35/75.45 ± 24.69/14.77 mmHg

Although most of the patients did not attain controlled blood pressure, all types of combinations of antihypertensive drugs that had been used, excluding the CCB with diuretic combination, showed a significant reduction in SBP and DBP measurements (Table IV). Combination of CCB and alpha blockers was the most effective in reducing SBP. SBP reduction is important as mentioned by Bakris *et al.* [16]. In a RENAAL study, baseline SBP of 140 to 150 mmHg was found to significantly increase risk for ESRF or death by 38% compared to those below 130 mmHg. Jafar *et al.* [26] also noted that progressive reduction of kidney function was in the lowest risk when SBP was between 110 and 129 mmHg. Addition of a BB into the same combination gave a greater decrease in DBP. From the study, the combination of CCB and diuretic was ineffective in reducing DBP although it was able to significantly reduce SBP. This suggested that combination of CCB and diuretics was more suitable to be used to reduce SBP without much influence on DBP. This is useful in isolated systolic hypertension cases where SBP is higher than 140 mmHg but DBP is lower than 90 mmHg. This finding is in agreement with Stokes [27] who stated that treatment of isolated systolic hypertension with diuretics, CCB and ACE inhibitor was effective in reducing systolic blood pressure and these agents may be used in combination to achieve the SBP goal of less than 140 mmHg. Bavanandan *et al* [28] found that to achieve a target DBP < 90mmHg, combination therapy is required in up to 57% of patients. Although the result showed combining antihypertensive drugs significantly reduce blood pressure, there were no significant difference in the SBP and DBP reduction between different combinations of antihypertensives. It indicated all combinations of antihypertensive drugs had similar effectiveness. The comparison of blood pressure reduction between different combinations of antihypertensive drugs did not show statistically significant difference among them because of insufficient samples for each type of combinations.

From the study, there was a positive medium correlation between them that was statistically significant. The result showed large SBP reductions in combination of CCB with alpha blockers and combination of BB, CCB and alpha blocker. Apart from that, both combinations also showed large reductions in DBP. It may indicate that when the SBP was reduced, DBP would also reduce. Chobanian *et al.* [6] stated most of hypertensive patients older than 50 years old would achieve targeted DBP if goal of SBP was achieved.

During the hospitalization, the creatinine clearance of hypertensive patients with ESRF showed an improvement. Creatinine clearance at the day of discharge was higher than the creatinine clearance at the day of admission. The result showed an improvement in creatinine clearance maybe associated with the controlled DBP of patients as Whitworth[24] stated that lowering DBP to less than 90 mmHg was associated with a slower rate of decline in GFR, and thus slowing down renal deterioration. Almost all the patients had DBP lower than 90mmHg during the hospitalization. Another factor that may influence improved creatinine clearance is the drugs that had been given to patients during hospitalization. From the overall improvement in creatinine clearance, it indicated that the drugs taken by patients during hospitalization did not worsen the patients' creatinine clearance. Most importantly, the findings suggested that, overall, antihypertensive drugs that were able to control blood pressure did not worsen patients' creatinine clearance.

Some common complications that can occur in hypertensive patients with ESRF include anemia, hypocalcaemia and hyperphosphatemia. Anemia is a hallmark of ESRF due to inadequate production in erythropoietin (EPO) in the kidneys, a hormone that is involved in production of red blood cells [11]. This was shown in the study where 84.1% of patients having hemoglobin less than 13.5g/dL for male and 12.0g/dL for female as the kidney function decreased. During hospitalization, some supplements were given to patients for anemia such as ferrous fumarate 200mg, folic acid 5mg and vitamin B complex either as a prevention or treatment approach.

From the study, the incidence of hypocalcaemia and hyperphosphatemia were high in ESRF patients. In fact, hypocalcaemia and hyperphosphatemia are two conditions that will often develop simultaneously when patients' kidney function continues to decrease. There were 51 patients with abnormalitites in calcium level which consisted of 49 patients with hypocalcaemia and 2 with hypercalceamia. For phosphate level, there were 61 patients who have phosphate level higher than normal range. In order to promote strong bone growth, our body needs balanced calcium, phosphorus and vitamin D levels. In ESRF patients with deteriorated kidney function, low calcitriol level will decrease intestinal calcium absorption while excessive secretion of parathyroid hormone can cause excessive calcium loss from the bones to compensate for low serum calcium level [29].

When the renal function is declined to 20% to 25% of normal, phosphorus excretion is not enough to accommodate the amounts that are absorbed by gastrointestinal tract. As a result, phosphorus retention occurs and hyperphosphatemia develops [29]. If serum phosphorus level rises to a level higher than 2.00 mmol/L, blood pressure and cardiac load will increase. Hyperphosphatemia is also associated with increased morbidity and mortality in ESRD patients [10]. Thus, effective control of serum phosphorus levels is a crucial clinical approach in managing hyperphosphatemia. According to Goodman [29], phosphate binders were commonly used to reduce phosphorus absorption, limit the amounts of phosphorus that enter the extracellular fluid and could be used as initial binder therapy. Patients included in this study who developed hyperphosphatemia during hospitalization were prescribed with calcium carbonate 500 mg as calcium-based phosphate binders in an effort to reduce phosphate levels as well as to increase serum calcium.

Limitations

The number of samples taken was only 107 patients. Some results that had shown non-significance or were different from other studies may have been caused by insufficient number of samples.

CONCLUSION

From the study, hypertension was one of the risk factor for ESRF. Combination of beta blocker and calcium channel blocker was the most common combination that was given to hypertensive patients with ESRF in this institution. Overall, combinations of antihypertensive drugs that were prescribed were effective in reducing blood pressure since there was significant decrease in blood pressure before and after taking antihypertensive drugs. However, the effectiveness between different combinations of antihypertensive drugs were not much different. The majority of patients had uncontrolled blood pressure. Combination of CCB and diuretic had the highest percentage of patients with controlled blood pressure. There was a medium correlation between systolic and diastolic blood pressure reduction. Besides that, creatinine clearance of patients generally showed improvement at the day of discharge. Anemia, hypocalcaemia and hyperphosphatemia were common complications detected in ESRF patients. Further study can be done on comparing different doses or different subclasess of antihypertensive drugs towards the reduction of blood pressure and the achievement of blood pressure control in hypertensive patients with ESRF. Effect of different combinations of antihypertensive drugs toward the creatinine clearance of the patients can also be studied in the future.

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REFERENCES

1. Abdul Rahman AR, Bavanandan S, Kamaruddin AS, *et al.* Clinical practice guidelines management of hypertension 3rd edition. MOH/P/PAK/156.08 (GU). Malaysia. 2008.
2. National Heart Association of Malaysia Third National Health and Morbidity Survey (NHMS) 2006. http://www.malaysianheart.org/article.php?aid=132 [14 August 2010].
3. National Kidney and Urologic Diseases Information Clearinghouse. Kidney and urology diseases statistic for the United States. http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/ [14 January 2010]
4. Wenzel RR. Renal protection in hypertensive patients: selection of antihypertensive therapy. Drugs 2005; 65(2): 29-39.
5. Cheung BMY, Lau CP & Kumana CR. Combination therapy for hypertension. Hong Kong Med. Journal 2003; 9(3): 224-5.
6. Chobanian AV, Bakris GL, Black HR, *et al.* Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 2003; 42: 1206-52.
7. Coresh J, Wei GL, McQuillan G, Brancati FL, *et al.* Prevalence of high blood pressure and elevated serum creatinine level in the United States. Arch Intern Med 2001; 161: 1207-16.
8. Julius S, Kjeldsen SE & Brunner H, *et al.* VALUE trial: Long term blood pressure trends in 13,449 patients with hypertension and high cardiovascular risk. Am J Hypertens 2003; 16: 544-8.
9. Williams, B. The year in hypertension. Journal of the American College of Cardiology 2008; 51 (18): 1803-17.
10. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children With Chronic Kidney Disease. American Journal of Kidney Diseases. 2005. suppl 1 46(4): 1-121.
11. National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. American Journal of Kidney Diseases. 2006. suppl 3 47(5): 1-146.
12. Manley HJ, McClaran ML, Overbay DK, *et al.* Factor associated with medication-related problems in ambulatory hemodialysis patients. Am J Kidney. 2003, 41: 386-93.
13. National Kidney Foundation. How your kidneys work. http://www.kidney.org/kidneydisease/howkidneyswrk. 2010. cfm [10 August 2010].
14. Ridao N, Luño J, Vinuesa SG, *et al.* Prevalence of hypertension in renal disease. Nephrology Dialysis Transplantation 2001;. 16(1): 70-3.
15. Hoffmann J, Comparison of felodipine – metoprolol combination tablets vs each component alone as antihypertensive therapy. The German Multicentre Study Group. Blood press 1993; 1: 30-6.
16. Bakris GL, Weir MR, Shanifar S, *et al,* RENAAL Study Group. Effects of blood pressure level on progression of diabetic nephropathy results from the RENAAL study. Arch Intern Med 2003; 163: 1555-65.
17. Bakris GL, Williams M, Dworkin L, *et al,* Preserving renal function in adult with hypertension and diabetes: A consensus approach. Am J Kidney Dis 2000; 36: 646-61.
18. Boiskin MM, Marcussen N, Kjellstrand CM, *et al.* Nephrotoxicity of ACE-inhibitors: Age and chronic renal failure increase the risk. Geriatric Nephrology and Urology 1995; 5(2): 71-7.
19. Brenner BM, Cooper ME, deZeeuw D, *et al.* RENAAL Study Group, Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy from the RENAAL study. N Eng J Med 2001; 345: 861-9.
20. Lewis EJ, Hunsicker LG, Clark WR, *et al.* Renoprotective effect of the angiotensin-receptor antagonist irbersartan in patients with nephropathy due to type 2 diabetes. N Eng J Med 2001; 345: 851-60.
21. Agoda LY, Appel L, Bakris GL, *et al.* Effect of ramipril vs amlodipine on renal outcomes in hypertension nephrosclerosis. A randomized controlled trial. JAMA 2001; 285: 2719-28.
22. National Kidney Foundation. High blood pressure and chronic kidney disease for people with CKD stages 1-4. 2009.
23. Neutel JM, The role of combination therapy in the management of hypertension. Nephrol Dial Transplant 2006, 21: 1469-74.
24. Whitworth JA. Progression of renal failure – the role of hypertension. Annals Academy of Medicine 2005, 34(1): 8-15.
25. Birchem JA, Fraley MA, Senkottaiyan N, *et al.* Influence of hypertension on cardiovascular outcomes in hemodialysis patients Seminars in Dialysis. 2005; 18(5): 391-5.
26. Jafar TH, Stark PC, Schmid CH, *et al.* Progression of chronic kidney disease: the role of blood pressure control, proteinuria and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann Intern Med. 2003.139: 244-52.
27. Stokes GS, Treatment of isolated systolic hypertension. Current Hypertension Reports. 2006. 8(5): 377-83.
28. Bavanandan S, Morad Z, Ismail O, *et al.* A comparison of valsartan and perindopril in the treatment of essential hypertension in the Malaysian population. Medical Journal of Malaysia 2005; 60(2): 158-62.
29. Goodman WG, Calcium and phosphorus metabolism in patients who have chronic kidany disease. The Medical Clinics of North America 2005;. 89: 631-47.