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RESEARCH ARTICLE

The effects of Amlodipine and Propranolol on Haemodialysis Efficiency in End-Stage Renal Failure patients

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ABSTRACT:

Background: The high rate of death and sickness perceived in patients with end-stage renal disease is principally ascribed to the inadequacy of haemodialysis (HD), and this may relate to inadequate analysis of the factors affecting the HD process, including drugs taken by these patients. **Aims and Objective:** To explore the potential association of a dihydropyridine calcium channel blocker (amlodipine) and a beta-blocker prototype (propranolol) separately with the dialysis efficiency in HD patients. **Methods:** This is a retrospective study which include 275 (112 females and 163 males, 83% of whom also suffered from hypertension) patients with end-stage renal failure on haemodialysis. Patients were categorized into three groups: 125 patients taking amlodipine, 81 patients taking propranolol, and 69 patients not taking any of the above medications (controls). The HD efficiency, and the percentage reduction in creatinine, uric acid, and urea levels were compared between groups. **Results:** Compared with patients who were not receiving amlodipine or propranolol, a significant increase in the major HD adequacy marker which is the Kt/V ratio, as well as in the percentage reduction in creatinine, uric acid, and urea levels, was observed in patients taking amlodipine, but a significant decrease in these markers was detected in patients taking propranolol. **Conclusions:** Taken together, these findings indicate that the haemodialysis efficiency may be significantly improved (diminished) by supplementation with amlodipine (propranolol).

KEYWORDS: Amlodipine, efficiency, haemodialysis, kidney failure, propranolol.

INTRODUCTION:

Renal replacement therapy via haemodialysis (HD) is the mainstay of management for patients with end-stage renal dysfunction[1]. Owing to the continuous advances in the HD techniques, annual death among these patients has declined in recent decades and presently ranges from 15% to 25%[2,3]. Consequently, high mortality and morbidity among chronic HD patients is mainly attributed to the insufficiency of dialysis[4,5,6]. HD therapy is considered efficacious if the patients are adequately relieved from uremia manifestations, and have a good nutritional status as well as sufficient production of red blood cells, conserve normal blood pressure, and the progress of neuropathy is avoided[7,8].

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Kt/V index, which points to the urea clearance during the HD session per unit of urea distribution volume, is documented as the main marker for dialysis efficiency[4]. Enhancement in Kt/V increases the elimination of the solute and thus reduces organ toxicity and the risk of systemic damage[7]. This marker can be elevated by improving the HD process by various means, including increasing the duration or frequency of HD sessions, using medium cut-off dialyzer and high-flux HD techniques, or prescribing intradialytic exercise to the patients[9-11]. However, most of the proposed methods cannot fully optimize the HD process[12,13]. As HD patients generally suffer from other comorbid conditions, such as cardiovascular disorders, hypertension, diabetes, hypocholesteremia, and obesity, they are prescribed a variety of medications that may influence their response to HD[14-16]. However, the potential correlation of these drugs with HD performance has never been investigated.

Given that blood flow significantly influences the flux of urea and accompanying toxins from the tissues to the systematic circulation, it also impacts the HD effectiveness[17]. It is well known that blood flow to peripheral tissues, including muscles, can be enhanced by calcium channel blockers (including amlodipine)[18], and can be reduced by beta-blockers such as propranolol[19]. Yet, the effects of these drugs that are widely used by HD patients on the performance of the haemodialysis process has never been investigated. These gaps in extant knowledge have motivated the present study, the aim of which is to explore the potential association of a dihydropyridine calcium channel blocker (amlodipine) and a beta-blocker prototype (propranolol) separately with the dialysis efficiency in HD patients.

METHODS:

This retrospective study involved 275 blood samples gathered from patients undergoing dialysis at the Urology and Nephrology Centre, King Khaled Hospital (Hail, KSA) prior to and following the HD session to determine the dialysis efficacy indices. For the purpose of comparative analyses, recruited patients were categorized into the following groups:

Group I: 125 patients (76 males and 49 females) taking amlodipine.

Group II: 81 patients (49 males and 32 females) taking propranolol.

Group III: 69 patients (38 males and 31 females) not taking any of the above medications, and thus designated as controls.

Prior to commencing the study, approval was obtained from the Ethics Committee of the Faculty of Medicine, University of Hail, Saudi Arabia (Ethical No.2018/0127). All participants provided written informed consent for the use of their results in this research. The blood samples were investigated for haemodialysis adequacy markers and drugs used by the patients.

Data collection:

After patients' records were reviewed for prescribed medications, statistical analyses were performed to determine whether associations exist between amlodipine and propranolol (separately) and HD performance. Effects of comorbid conditions (such as cardiovascular disorders, hypertension, diabetes, hypocholesteremia, and obesity) as well as other influential factors, such as patient age, gender, socioeconomic status (income, education level, living conditions, etc.), and duration of end-stage renal disease were also examined. All HD efficacy indicators (i.e., Kt/V, urea reduction ratio, creatinine reduction ratio, and uric acid reduction ratio) were assessed.

Calculation of HD efficacy parameters:

Blood samples were taken immediately prior and after the HD session following a standard protocol. These samples were subjected to kidney function and uric acid tests as described in our previous works[20,21]. A single-pool spKt/V (was determined from pre- and post-HD blood urea nitrogen (BUN) values according to the Daugirdas second-generation formula[22]: $Kt/V = -\ln(R - 0.008 * t) + (4 - 3.5 * R) * UF/W$

where R represents the ratio of the post-HD to pre-HD BUN concentration, t designates HD management time in hours, UF means the volume of fluid removed during the HD treatment in litters, and W specifies the post-HD body weight in kilograms.

The BUN, creatinine and uric acid reduction ratios (URR, CRR, UARR respectively) were calculated from pre- and post-HD concentrations of these markers according to the following formula:

Marker reduction ratio = [marker pre hemodialysis - marker post hemodialysis/ marker pre hemodialysis] × 100%

Statistical analysis:

All data were analyzed using the SPSS program version 20 and the results were expressed as mean (M) ± standard deviation (SD). One-way analysis of variance (ANOVA) followed by Duncan post hoc test and/or t-test was utilized in the analyses. Pearson's relationship coefficient was calculated to evaluate the correlations, with $p < 0.05$ indicating statistical significance.

RESULTS:

The sample for the present study included 275 hemodialysis patients (112 females and 163 males) aged between 25 and 83 years (median = 51 years), 139 of whom were diabetics and 136 non-diabetics, and 229 of the recruited patients were hypertensive and the remaining 46 were not. As 125 patients were taking amlodipine, and 81 were taking propranolol, 69 patients that were not taking either drug were treated as controls in the analyses (Table I).

Table I. Demographic data of patients

		Percent
Age (M ± SD)	51.09 ± 17.07	
Range	25 - 84	
median	53	100
Number	275	41/59
M/F	112/163	51/49
Diabetic/Non	139/136	
Diabetes (type I/ type II)	105/34	38/12
Hypertensive/Non	229/46	83/17
Treatment		
Amlodipine	121	44
Propranolol	78	28.4
Non (control)	76	27.6

Amlodipine effects:

The study findings revealed that patients receiving amlodipine had reduced kidney function blood markers (as indicated by all the measured values) relative to controls. Specifically, a significant decrease in the pre-dialysis creatinine, uric acid, and urea levels was observed in the treated group (768.5±90.1, 5.91±1.12, and 19.68±3.09) versus the control group (792.2±85, 6.22±1.26, and 23.73±6.53, p = 0.034, 0.036, and 0.001, respectively). Similarly, the post-dialysis levels of creatinine, uric acid, and urea were significantly reduced in the treatment group (316.3±63.5, 2.04±0.75, and 6.19±2.64, respectively) vs. the control group (335.4± 69.4, 2.23±0.56, and 7.15±3.11, p = 0.024, 0.029, and 0.01, respectively).

The percentage reduction in creatinine, uric acid, and urea between pre-dialysis and post-dialysis levels in the treatment group was calculated at 58.84±6.65%, 65.48± 12.14%, and 68.54±8.96%, respectively, whereas much lower values were obtained for the control group, at 56.95±5.53%, 62.14±6.45%, and 65.91±9.44% (p = 0.019, 0.023, and 0.025, respectively) (Table II).

Table II. Effect of Amlodipine and Propranolol on kidney function and percent of the reduction.

Parameters	Treatment		
	Amlodipine (n= 121)	**Propranolol (n= 78)**	**Control (No treatment) (n = 76)**
Pre-dialysis Creatinine	768.5 ± 90.1 (p = 0.034)	821.9 ± 116 (p = 0.031)	792.2 ± 85
Uric acid	5.91 ± 1.12 (p = 0.036)	6.57 ±1.03 (p = 0.03)	6.22 ± 1.26
Urea	19.68 ± 3.09 (p =0.001)	26.07 ± 7.23 (p = 0.018)	23.73 ± 6.53
Post-dialysis Creatinine	316.3 ± 63.5 (p =0.024)	360.8 ± 78.5 (p =0.016)	335.4 ± 69.4
Uric acid	2.04 ± 0.75 (p = 0.029)	2.45 ± 0.87 (p =0.032)	2.23 ± 0.56
Urea	6.19 ± 2.64 (p =0.01)	8.83 ± 4.66 (p =0.004)	7.15 ± 3.11
Percent reduction Creatinine	58.84 ± 6.65 (p =0.019)	54.88 ± 4.73 (p =0.007)	56.95 ± 5.53
Uric acid	65.48 ± 12.14 (p =0.023)	59.56 ± 7.74 (p =0.013)	62.14 ± 6.45
Urea	68.54 ± 8.96 (p =0.025)	62.59 ± 11.12 (p =0.024)	65.91 ± 9.44

Comparison was done between each treatment group against the control.

*Significant with respect to no treatment (t-test), Reduction = $\frac{\text{(Pre-dialysis – post dialysis)}}{\text{Predialysis}} \times 100$ expressed as percent ± SD

Propranolol effects:

In the propranolol-treated group, the pre-dialysis levels of creatinine, uric acid, and urea (821.9±116, 6.57± 1.03, and 26.07±7.23, respectively) were significantly increased relative to the controls (p = 0.031, 0.03, and 0.018, respectively). Likewise, the post-dialysis levels of creatinine, uric acid, and urea were significantly increased in the treated patients (360.8±78.5, 2.45± 0.87, and 8.83±4.66) compared to the controls (p = 0.016, 0.032, and 0.004, respectively). However, a significant decrease in the percentage reduction in these markers was noted (54.88±4.73%, 59.56±7.74%, and 62.59± 11.12%, p = 0.007, 0.013, and 0.024, respectively), as shown in (Table II).

Efficiency of dialysis (Kt/V):

Patients who were treated with amlodipine had a significant increase in Kt/V (1.45±0.37, p = 0.016) compared to controls (1.35±0.21), while in those receiving propranolol, the HD efficiency declined significantly (to 1.26±0.36, p = 0.03) in comparison to the control group, as shown in (Figure 1).

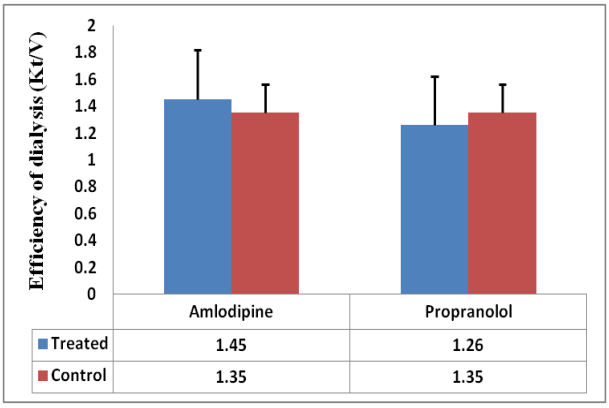

Figure 1- Efficiency of dialysis in patients treated with amlodipine and propranolol.

Kt/V = 1.162 × ln post(BUN)/pre(BUN), BUN: bound urea nitrogen.

DISCUSSION:

The findings yielded by the present study revealed a significant enhancement in all tested indices of HD adequacy among patients treated with amlodipine compared with the control group, whereas propranolol had the opposite effect. It is well known that substantial quantities of urea and creatinine are deposited in low-perfusion tissues such as bones, skeletal muscles, and skin[23]. Therefore, the effects of amlodipine and propranolol observed in this study may potentially be attributed to the opposing effects of these medications on blood vessels, as amlodipine induces vasodilation and propranolol promotes vasoconstriction[19]. Moreover, unlike propranolol, amlodipine enhances blood flow in the tissues and opens the capillary surface area, which increases the flux of urea and creatinine from these

tissues (including the skeletal muscles) to the systemic circulation[19]. This surge, in turn, may increase serum urea and creatinine elimination, and thus enhance HD efficacy. Consequently, the significant improvements in Kt/V and other indices detected among HD patients supplemented with amlodipine in this study were expected. These findings clearly indicate that supplementation with amlodipine (and other dihydropyridine calcium channel blockers) can be beneficial to HD patients as it has the potential to improve the dialysis efficacy. The results reported in this work are in line with the findings obtained by other authors signifying that treatment with calcium channel blockers is related to a lower mortality hazard[23,24]. Conversely, significant deteriorations in spKt/V, URR, and CRR were detected among patients treated with propranolol, countering the evidence produced by Jin et al. suggesting that β-blockers are linked to diminished fatality in dialysis patients[25].

Nonetheless, our results related to propranolol are supported by those reported by Omae et al., who found that beta-blockers did not improve endurance and even worsened the cardiovascular prognosis in dialysis patients[26]. These inconsistencies may be attributed to the differences in the drugs being studied (e.g., carvedilol causes vasodilation while propranolol has the opposite effect). Beta-blockers (particularly non-selective agents, including propranolol) decrease cardiac output and induce vasoconstriction, thereby diminishing blood flow, which may explain the reduction in the dialysis efficiency.

Moreover, many investigators have measured Kt/V, URR, and CRR values in patients undergoing acute or long-term intradialytic exercise programs and observed enhancement of HD adequacy in this cohort. Importantly, these effects were ascribed to an increase in muscle perfusion induced by intradialytic exercise[27-29], which supports the current results.

Furthermore, our results indicate that in patients treated with amlodipine the blood concentration of creatinine and urea was significantly lower compared with controls both before and after the dialysis session. Conversely, patients treated with propranolol had significantly higher serum levels of creatinine and significantly elevated urea compared with controls at both measuring points. As our patients were taking these medications chronically and were undergoing haemodialysis for at least two years, these results may indicate the cumulative effects of these drugs on HD adequacy.

On the other hand, our analyses revealed that patients treated with amlodipine had lower basal plasma levels of uric acid compared with controls, whereas opposite findings were noted for patients receiving propranolol. These results are supported by available evidence indicating that higher uric acid blood levels decrease HD efficacy[30]. Therefore, further studies are urgently needed to establish whether amlodipine and propranolol exert their influence on HD through direct effects on the blood vessels, or indirectly via uric acid, or via both mechanisms.

CONCLUSIONS:

Taken together, the results reported here indicate that treatment with amlodipine could significantly enhance, while propranolol supplementation may significantly diminish, the HD efficiency in end-stage renal diseases patients. It is also hoped that this study will motivate further investigations involving other medications used by HD patients and their role in the HD efficiency and accordingly the health, quality of life, and rate of mortality in these patients.

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DECLARATIONS:

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CONFLICT OF INTEREST:

The author has no conflicts of interest to declare.

ETHICAL APPROVAL:

The study was approved by the Institutional Ethics Committee.

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