

The Effect of Exforge-HCT on Blood Pressure Control in Omani Hypertensive Patients Attending Sultan Qaboos University Hospital

Ali AlSharqi^{1,*}, Halima Aal Homouda¹, Tariq Al-Saadi², Khamis Al Hashmi³

¹Medical Student, Sultan Qaboos University, Muscat, Oman

²Neurosurgical Resident, Montreal Neurological Institute and Hospital - McGill University, Montreal, Canada

³Department of Physiology & Clinical Physiology, Sultan Qaboos University, Muscat, Oman

*Corresponding author: ali.sharqi95@gmail.com

Abstract Background: Hypertension is worldwide health burden. The major concern about hypertension is that it is usually asymptomatic until it causes end organ damages. The management of hypertension usually starts with monotherapy which fails in achieving targeted BP control in many patients. Therefore, they are switched to combination therapy. Fixed combination therapy is proven to be more effective in controlling hypertension than free combination therapy. Exforge-HCT is a fixed combination drug consisting of Amlodipine, Valsartan and Hydrochlorothiazide. Its effectiveness is not known in Omani hypertensive patients. **Aim:** To evaluate the role of exforge-HCT in control of blood pressure in Omani hypertensive patients attending SQUH and its effectiveness based on gender. **Method:** This is a retrospective study. Data was gathered using HIS from January 2013 to June 2016. Patients taking Exforge-HCT were screened for eligibility for the study. Blood pressure measurements before and after using Exforge-HCT were recorded. Patients were grouped according to gender, number of co-morbidities and number of medications used before EXFORGE-HCT into two groups; group one: those who were on triple free drug combination therapy and group two: those who were on dual free drugs. P value of less than 0.05 was considered significant. **Results:** Total number of patients was 115 with female being 57% and male being 42%. The Level of control of hypertension increased from 22% to 33%. Over all Significant reduction in blood pressure was observed, but there was no gender difference in response to Exforge-HCT. There was significant difference in the response to Exforge-HCT between the medication groups but the response according to gender in each group remains the same. Response to Exforge-HCT was the same regardless the number of co-morbidities in both gender. **Conclusion:** Exforge-HCT showed significant reduction in BP but no gender difference in response. There was significant difference in the response between the two medication groups. However, the response between genders remains the same in each co-morbidity and medication group. Further prospective study is needed to confirm these findings.

Keywords: Exforge-HCT, Hypertension, Oman, control, fixed combination

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1. Introduction

Hypertension is a disease in which the blood vessels have chronically increased pressure which is equal to or over 140 mmHg when the heart contracts (systolic) and/or equal to or over 90 mmHg when the heart relaxes (diastolic). Hypertension is known as "silent killer" since most patients are asymptomatic. However, some patients may experience headache, shortness of breath, chest pain, dizziness, palpitation and nose bleeds [1].

Essential Hypertension is a major public health problem. Pathogenesis is not fully understood. Disorder of Heterogeneity is a characteristic of the essential hypertension; the Blood pressure (BP) rise is due to

different causes that spread among wide variety of patients. It is associated with renal dysfunction with unknown cause. However, obesity seems to play a role in developing hypertension [2]. The major concern about hypertension is that it is usually asymptomatic until it causes an end organ damage which happens due to increased hemodynamic load [3]. By searching and reviewing the published literature from 1980 to 2002, Kearney and partners estimated the worldwide burden of hypertension. They concluded that around 26.4% of the worldwide adult population had hypertension and predicted that this would increase to 29.2% by 2025 [4]. The condition in Oman is more or less the same as it was estimated to be 25.4% in 2008 according to the World Health Organization (WHO) [5]. Majority of these patients are inadequately controlled. According to Framingham Heart Study which included

1959 patients, around 71.0 % of subjects were inadequately controlled in both systolic and diastolic BP [6]. A study was conducted in 2011 in primary health care (PHC) in Wilayat Al Seeb showed that BP in more than 60% of hypertensive patients are inadequately controlled [7]. In the past 10 years, prevalence of heart failure and the incidence of end-stage kidney disease had increased. Inadequate control of BP in the hypertensive patients is a main contributor to these trends [2]. This is a major concern since hypertension is one of the main causes of heart diseases, which are the leading cause of death in Oman according to World Health Organization [5]. Therefore; adequate control of BP is an important step to reduce cardiovascular mortality and morbidity.

More than 95 % of patients with hypertension are classified as having essential hypertension. This non-specific diagnosis may lead to a major problem with non-compliance and suboptimal therapeutics. So, to a better Understanding of the nature of the disease; the normal control of blood pressure (BP) is a must be understood. The regulation of BP is a very complicated physiological function, dependent on multiple mechanisms that work together in a continuum manner to ensure that the BP return to the normal range, including; renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, and several humeral factors like vasopressin and atrial natriuretic peptide (ANP). These mechanisms either act on the kidney by changing the body fluid status through increasing or decreasing water and salts reabsorption and therefore changing the blood volume and/or act on the blood vessels by changing their diameter through vasoconstriction and vasodilatation action therefore controlling BP [8].

There are different types of drugs which aim to reduce BP. These include diuretics, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs). These drugs work either by increasing water excretion and/or decreasing peripheral resistance or the cardiac output to decrease BP [9]. The management of hypertension usually starts with monotherapy. However, most patients fail to reach an adequate control of BP by using single drug. Therefore, combination of multiple drug classes is required [10]. Combination therapy of BP lowering medication, should act in complementary mechanisms, leading to an additive BP decreasing effect. Different studies were conducted to evaluate the effectiveness of combination therapy in controlling hypertension. In a study that conducted to compare between valsartan (ARB)/hydrochlorothiazide (diuretics) combination therapy and monotherapy, a greater decline in BP with cooperative mechanism of fixed combination therapy was reported than with monotherapy [11]. Other study showed that the triple therapy was more effective than the dual therapies in controlling both systolic and diastolic BP [12]. A meta-analysis published in 2013 showed that combining drugs with different mechanisms of action has approximately five times more reduction in BP than increasing the dose of a single drug [13]. This concludes that Antihypertensive regimens which include two or more drugs have significant control in BP than the single-agent does.

The advantages of using fixed-combination drugs include effective control of BP, reducing the adverse

effects of the drug, longer duration of drug's action and broad spectrum of response to the drug [14]. They can also improve the adherence and reduce pill's load which improve the psychological condition of the patients. Furthermore, the fixed combination is less expensive than free combination [15]. However, Fixed-combination drugs are less flexible in dose adjustment and can raise the risk of drug to drug interactions. In addition, a study has shown that there is increased risk of cardiovascular and renovascular events and mortality with increased BP variability. Using combination therapy was proven to reduce BP variability [16]. Moreover, in fixed combination, the dose of each medication is usually lower than the regular monotherapy management, making it hard to achieve the effective dose that is required for the management [15].

Exforge-HCT is one of the fixed-combination drugs that are available in Sultan Qaboos University-Hospital (SQUH) and prescribed to the primary hypertensive patients. Exforge-HCT is a fixed combination of Hydrochlorothiazide (HCTZ), Amlodipine (Aml) and Valsartan (Val), which they act as a thiazide diuretic, an ARB and CCB respectively [17]. A study compared between Val/HCTZ combination and monotherapy showed that the incidence of hypokalemia was higher with HCTZ monotherapies than VAL/HCTZ combinations [11]. Another study was done to compare the effect of Aml/Val+HCTZ free drug combination and Aml+HCTZ drug combination on controlling BP. The results showed higher BP control with Aml/Val+HCTZ free drug combination [14]. These conclude that triple free combination therapy is better in BP control than the dual. However, to the best of our knowledge, there is no study done in Oman to determine the effectiveness of the Exforge-HCT in Omani population and there was no study to correlate the use of Exforge-HCT and its effect on different sex. Therefore, the rationale for conducting this research is to shed the light on the control of BP among Omani hypertensive patients who attend SQUH and utilize Exforge-HCT and to compare the response between free and fix combination of the same drug classes. Moreover, to evaluate the effect of number of medications and comorbidities on BP control.

2. Goal of the Project

The goal of this study is to evaluate the role of Exforge-HCT on BP control in Omani hypertensive patients who attended Sultan Qaboos University Hospital (SQUH).

3. Specific Objectives

- To evaluate the effect of gender on BP response to Exforge-HCT.
- To assess the difference in BP response when switching the medications from two or three free combination therapy to fix therapy (Exforge-HCT) in both gender.
- To evaluate the effect of number of comorbidities on BP response to Exforge-HCT in both gender.

5. Methods and Study Design

5.1. Study Design

A cohort study in the form of retrospective was conducted in the period of February 2016 to January 2017 in SQUH which is a tertiary hospital in Muscat, Saltant of Oman.

Ethical approval was obtained from the College of Medicine and Health Sciences ethics committee. Moreover, the access authorization to the hospital electronic medical records was provided by the Hospital Information System (HIS).

5.2. Study Setting and Sampling

5.2.1. Recruitment

List of Omani hypertensive patients who attended SQUH from January 2014 to July 2016 and utilized Valsartan, Amlodipine and Hydrochlorothiazide on fixed combination was generated by the HIS and the patients were identified and evaluated for eligibility.

5.2.2. Inclusion Criteria

The study included Omani hypertensive patients who are older than or equal to 18 years of age and were on a double combination management (free or fixed combination) or a triple free medication and then switched to Exforge-HCT. Those patients should have regular follow up at the SQUH outpatient clinic for at least 6 months per year and their BP regularly checked up and recorded. They did not change the class or the dose of other antihypertensive medications after switching to Exforge-HCT. The patients were selected regardless of their other co-morbidities or other drugs use for different diseases.

5.2.3. Exclusion Criteria

Patients who had no medication history or who did not meet with the inclusion criteria were excluded.

5.2.4. Data Collection

The data was collected by using TrackCare system. All patients who attended SQUH in the period of January 2014 - July 2016 and met the inclusion criteria were included in the study. Demographic data including gender, age, weight, and height were gathered. Two measurement of BP were taken; one before the utilization of Exforge-HCT (baseline) and the other after utilization of Exforge-HCT. The BP measurement should be within 3-6 month of the utilization of Exforge-HCT. The following information was also collected; the number and type of the other drug consumed, lipid profile and the co-morbidities which included; heart failure, ischemic heart disease, chronic renal disease, stroke and diabetes.

5.2.5. Subjects

All patients who were on Exforge-HCT were screened for the eligibility of the study. The total number of patients was 615 initially. However, 178 of the patients were excluded because they had no drug history, 136 patients did not have one or both of BP measurements recorded in the system and 52 patients were not Omanis.

Also, 143 patients had not met with the drug history requirement before using Exforge-HCT. Therefore, a total number of 500 patients were excluded. Ultimately, 115 patients were eligible for the study and included in the final analysis.

5.3. Data Analysis

The data was analyzed using IBM Statistical Package for the Social Sciences (SPSS) 23 computer program. Frequency tables were used to find the mean and standard deviation for age, body mass index (BMI) and both systolic and diastolic BP. The patients were categorized according to gender (male and female). SBP and DBP were tested for the normality of distribution by using one sample Kolmogorov- Smirnov test (K-S test). Since diastolic blood pressure (DBP) was following normal distribution, paired sample t test was used to evaluate its significant difference before and after utilizing Exforge-HCT among gender. However, because systolic blood pressure (SBP) was not following normal distribution, wilcoxon signed rank test was used to evaluate its significant difference before and after utilizing Exforge-HCT among gender. Moreover, the patients were grouped according to the number of antihypertensive medication that they were using before utilizing Exforge-HCT into two groups: group 1 (triple antihypertensive free medications therapy) and group 2 (dual antihypertensive free medications therapy). The significant in the reduction in both DBP and SBP was used to analyze the deference in the response to Exforge-HCT between the two groups among both genders. In order to assess the difference in the response to Exforge-HCT in DBP between the two groups among gender, independent sample t-test was used. Furthermore, Mann-Whitney U test was used to evaluate the difference in the response to Exforge-HCT in SBP between the two groups among gender. The patients were further divided according to the number of co-morbidities into three groups: group 1 (no comorbidity), group 2 (one comorbidity) and group 3 (two or more comorbidities). To evaluate the difference in the response to Exforge-HCT in DBP between the three groups among gender, One-way ANOVA was used. Additionally, Kruskal-Wallis test was used to evaluate the difference in the response to Exforge-HCT in SBP between the three groups among gender. P value of < 0.05 was considered for the statistical significance.

6. Result

6.1. Descriptive Statistics

The demographic information for the subjects participated in the study is shown in [Table 1](#). There was a total number of 115 patients with a mean age of 61.8 ± 11.8 years. There were more female patients than the male patients accounting for 66 (57.4%) and 49 (42.6%) respectively. The mean BMI for males was 30.7 ± 5.4 kg/m² and for females was 32.5 ± 6.6 kg/m². Before starting the medication, 20.9 % of patients (N=24) were controlled (SBP < 140 and DBP < 90). However, this percentage increased to 33.0 % (N=38) after starting Exforge-HCT.

The average DBP before starting Exforge-HCT was 83.0 ± 13.0 mmHg and after the utilization, the average decreased to 78.6 ± 13.0 mmHg. The median SBP before starting the medication was 158.0 mmHg with a maximum

value of 220.0 mmHg and minimum value of 117.0 mmHg and after starting the medication the median SBP dropped to 148.00 mmHg with a maximum value of 199.0 mmHg and a minimum value of 117.0 mmHg.

Table 1. Demographic and clinical characteristics

Variables (unit)		Number (%)	Mean \pm SD	Median
Nationality	Omani	115 (100%)		
	Non-Omani	0 (0%)		
Gender	Male	49 (42.6%)		
	Female	66 (57.4%)		
Age (years)		115 (100%)	61.8 ± 11.8	
BMI(Kg/m ²)		89 (77.4%)	31.7 ± 6.1	
Average SBP (mmHg)	Before	115 (100%)		158
	After			148
Average DBP (mmHg)	Before	115 (100%)		83.0 ± 13.0
	After			78.6 ± 13
Level of controlled patients	Before	24 (20.9%)		
	After	38 (33%)		

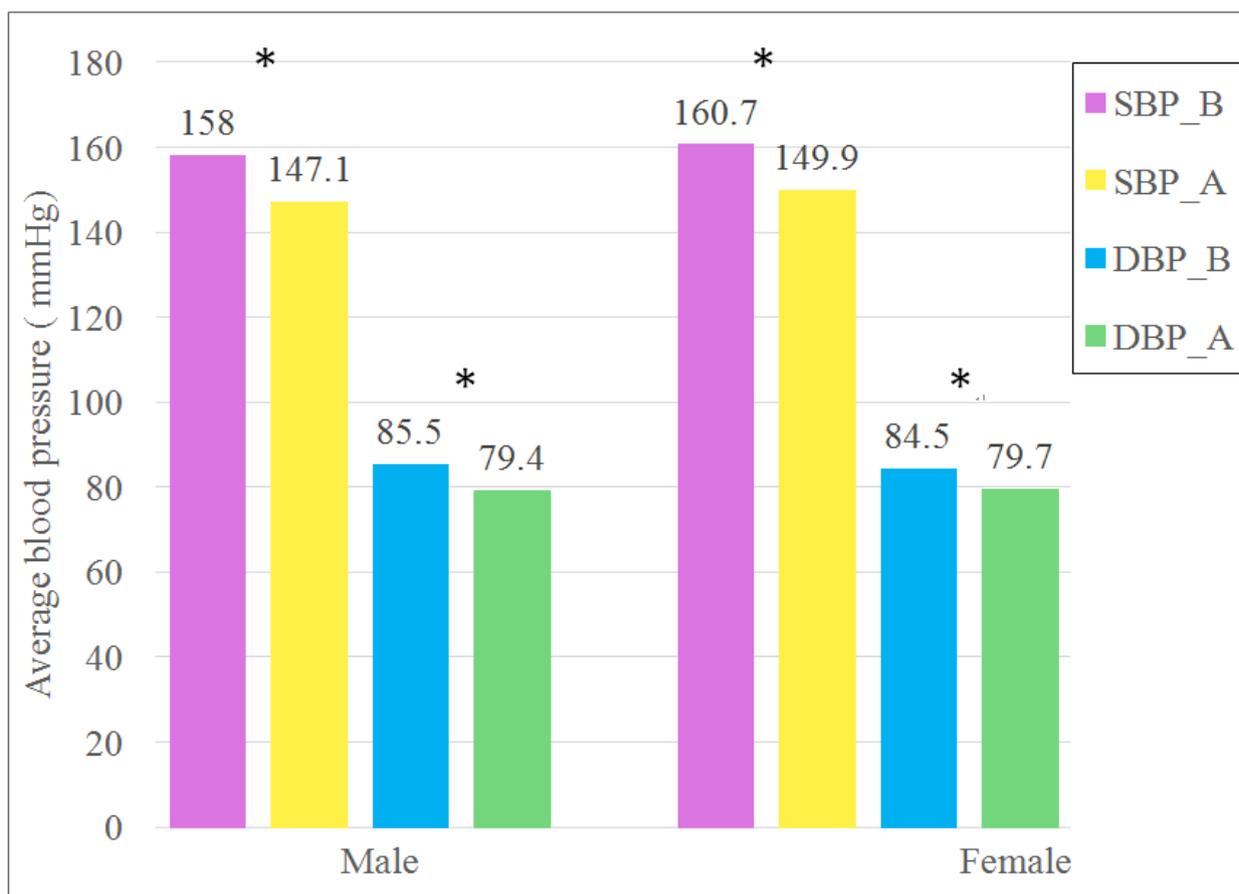


Figure 1. Difference in blood pressure before and after the starting Exforge-HCT among gender (*= P value < 0.05)

6.2. The Difference in Average BP before and after the Utilization of Exforge-HCT in Both Genders

Figure 1 represents the BP difference among the males and females. As it is shown in the figure, there was significant reduction in both DBP and SBP in both males and females with a P value of < 0.05. The analyses for

DBP showed the following: in the male group, the reduction was from 85.5 mmHg to 79.4 mmHg in the average DBP (Δ difference = 6.1 mmHg) whereas in the females, the mean difference was 0.9 mmHg. Furthermore, the analyses of SBP showed a mean deference of 10.9 mmHg in the males and a mean difference of 10.8 mmHg in the females. However, there was no significant difference in the response to Exforge-HCT between gender; p value > 0.05.

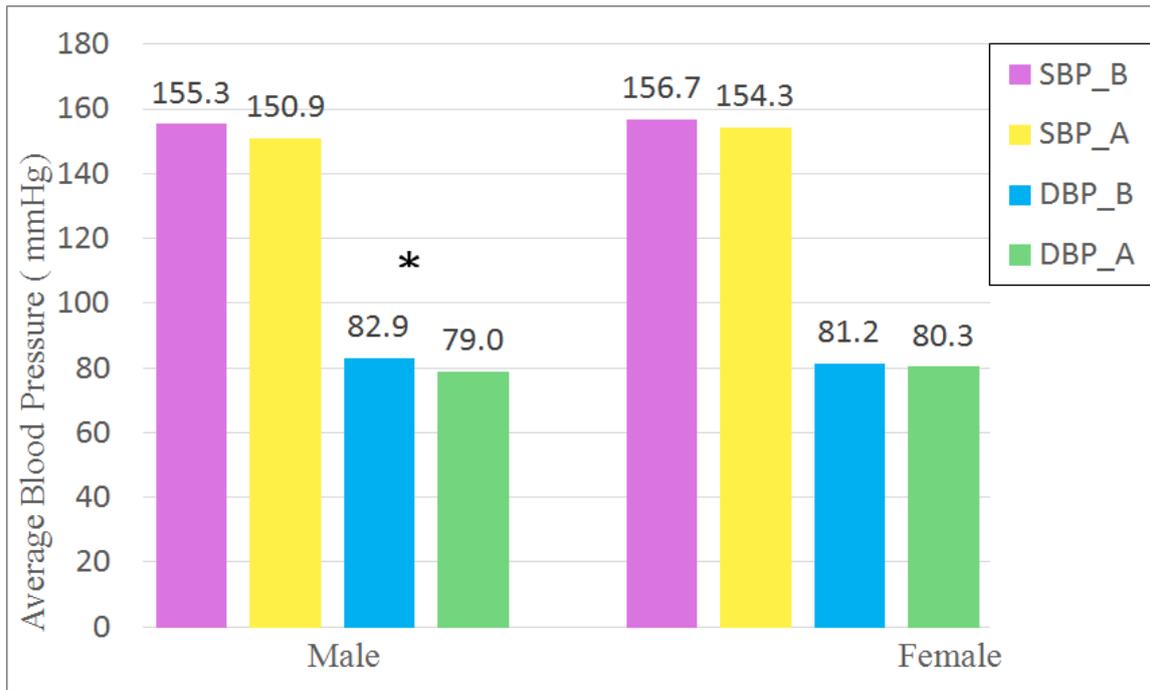


Figure 2. Difference in blood pressure before and after the starting Exforge-HCT in patients who were on triple free antihypertensive combination therapy (*= P value < 0.05)

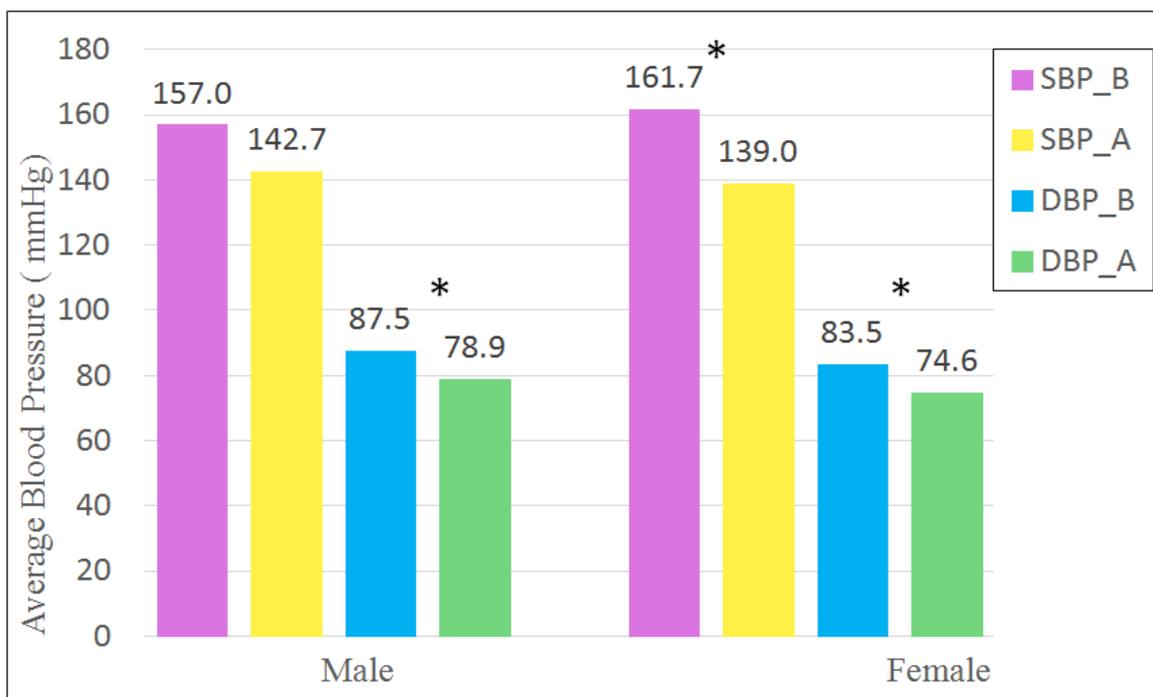


Figure 3. Difference in blood pressure before and after the starting Exforge-HCT in patients who were on dual free antihypertensive combination therapy

6.3. The Difference in BP before and after the Utilization of Exforge-HCT among Gender according to the Number of Medications

Group 1:

Figure 2 illustrates the difference in BP before and after the utilization of Exforge-HCT based on gender in group 1 (triple antihypertensive free medications therapy). Regarding the DBP, the results were as the following for each gender.

In the male group, there was a significant reduction in the average DBP (Δ difference= 3.9 mmHg and P value < 0.05). In the females group, there was no significant difference; (Δ difference= 0.9 mmHg and P value 0.568). Furthermore, the analyses for SBP showed that, in the males group, there was no significant difference in the average SBP before and after the utilization of Exforge-HCT (Δ difference= 4.4 mmHg and P value = 0.214). Also, we found that there was no significant difference in the female group; (Δ difference= 2.4 mmHg and P value = 0.717).

Group 2:

Figure 3 shows the difference in BP before and after using Exforge-HCT among gender in group 2 (dual antihypertensive free medications therapy). Regarding the DBP, the results were the following for each gender. In both group the reduction in average DBP was significant with a P value of < 0.05 . For the male group the average difference was 8.6 mmHg and for the females group the average difference was 8.9 mmHg. Furthermore, the analyses for SBP demonstrated the following: in the male group, there was no significant difference in average SBP before and after utilizing Exforge-HCT (Δ difference= 14.3 mmHg and P value = 0.118). Moreover, in the female group, the reduction was significant (Δ difference= 22.7 mmHg and P value < 0.05).

There was a significant difference in the response to Exforge-HCT between patients who were on dual antihypertensive medication and those who were on triple antihypertensive medication in both systolic and diastolic BP with a p value < 0.05 . However, in each group there was no significant difference in the response to the medication between male and female patients in both systolic and diastolic BP; p value > 0.05 .

6.4. The Difference in BP before and after the Utilization of Exforge-HCT in both Genders according to Different Group of Comorbidities

As shown in Table 2, regardless the number of comorbidities, there was no significant reduction in both SBP and DBP in all groups; p value > 0.05 . However, there was a significant reduction in both SBP and DBP in females who had one comorbidity; for SBP (Δ difference= 11.6 mmHg and P value = 0.004) and for DBP (Δ difference= 4.4 mmHg and P value = 0.017). Furthermore, the analysis showed that there was no significant difference in the response to Exforge-HCT between the patients regardless of the number of co-morbidities in both diastolic and systolic blood pressure; p value > 0.05 . Moreover, in each comorbidity group, there was no significant difference in the response to the medication between male and female patients in both diastolic and systolic blood pressure; p value > 0.05 .

Table 2. Difference in blood pressure before and after the utilization of Exforge-HCT in both gender according to different groups of comorbidities

Comorbidity group	Gender	Average diastolic blood pressure	P value	Average systolic blood pressure	P value
		Δ difference (mmHg)		Δ difference (mmHg)	
Group 1	Male	5.5	0.152	11.7	0.101
	Female	- 0.4	0.876	0.7	0.888
Group 2	Male	4	0.108	2.6	0.754
	Female	4.4	0.017	11.6	0.004
Group 3	Male	7.1	0.082	10.5	0.148
	Female	7.1	0.195	15.4	0.168

7. Discussion

The main aim of the study was to evaluate the role of Exforge-HCT on BP control in Omani hypertensive patients who attended SQUH. The level of BP control before starting the medication was 20.9 % and this percentage slightly increased to 33.0 %. Similarly, a study showed that the level of control in BP when using fixed combination improves from 36.8% to 54%. This result might be due to increase compliance to the medications. This is supported by a study that was published in 2013 included 7224 patients showed that fixed combination drug therapy has better compliance and persistence which ultimately lead to better control of BP compared to free combination drug therapy [16]. Despite the use of Exforge-HCT, control rates remain poor. This level of BP control was also observed in studies that showed the level of inadequately controlled hypertension in United State was 61% and in Europe was 88% of Polish [18]. The same situation applies here in Oman as it was estimated that more than 60% are inadequately controlled according to the Al-saadi's study [7]. Among the other causes for uncontrolled hypertension, non-compliance to the anti-hypertensive medication may have a substantial contribution in this finding.

There was significant reduction in both diastolic and systolic blood pressure in both gender and their response to Exforge-HCT was the same. This is in contrast with a study that found women to be more responsive to anti-hypertensive medication than men [19]. The small sample size might be the reason behind this finding.

As it was illustrated previously, we found that there was significant reduction in the DBP in male patients who were on triple free antihypertensive medications and switched to Exforge-HCT. A study done in Saudi Arabia shows that males have poor diastolic blood pressure control compare to females [20]. This result can be explained due to the fact that the males in our study have a mean age which is lesser than the females. Additionally, the small sample size might affect the accuracy of the results and make it difficult to draw a solid conclusion. In group 2, the male patients still had significant reduction in DBP whereas female patients showed significant reduction in both systolic and diastolic blood pressure. This finding is combatable with a study done in china that shows females have better control in both systolic and diastolic BP than men [21]. This is might be attributed to the hormonal factors and the fact that women tend to have less cardiovascular comorbidities than men which lead to better BP control [22].

Moreover, there was significant difference in the response to Exforge-HCT between the two medication groups with second group showing a better response. This was expected since those patients were on two medications and switch to Exforge-HCT which included further more drug so eventually there will be three different medication work cooperatively to decrease the BP more than what the two medication did and since Exforge-HCT is only one pill, there will be improvement in adherence.

As detailed in the result section, the same response to the drug according to the number of co-morbidity was observed in both genders. Similarly, Sarkar et al evaluated the role of number of co-morbidity in BP control and

found that the BP control is the same regardless the number of co-morbidity [23]. As the matter of fact, increasing the number of co-morbidities does not affect the compliance as Saadat et al showed in their study[24]. Furthermore, there was significant reduction in both systolic and diastolic blood pressure only in females who had one co-morbidity. However, there is a lack of supportive scientific research to explain this result. One speculation that with increasing number of different diseases, the patients become more concern about his health and therefore more adherence and persistence to the medications. In addition, the hormonal difference may explain this result. A study found that estrogen cause salt insensitivity in women and by this mechanism it helps in reducing the kidney response to salt thereby reducing the BP [22].

8. Limitation

The study has many limitations as any other retrospective study. Missing history data is one limitation. Lack of generalizability is also another limitation which happened due to the limited number of patients and only one hospital included in the study. Moreover, 24 hour ambulatory BP monitor must be used and in this study used clinic BP.

9. Conclusion

Using Exforge-HCT shows better BP control in Omani hypertensive patients who attended SQUH. Overall, males and females had similar response to the drug. In addition, there was significant difference in the response to the drug between the patients who were on dual free drug therapy and those who were on triple free drug therapy and switched to Exforge-HCT. However, the response is the same in both males and females in each group. Regardless the number of comorbidity, the response to the medication remains the same in both genders.

These findings indicate that the response is unlikely to be due to the gender difference. However, we recommend doing prospective study to have more accurate result and prevent the problem of missing data. Also, the study should be further carried out to increase the sample size and this can be done by including patients from different hospitals from all over Oman.

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