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Comparative Efficacy of Irbesartan/Hydrochlorothiazide and Valsartan/Hydrochlorothiazide Combination in Lowering Blood Pressure: A Retrospective Observational Study in Oman

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Key Words
Irbesartan · Valsartan · Hypertension · Diabetes mellitus · Nephropathy

Abstract
Objective: To compare blood pressure (BP) control in patients receiving irbesartan/hydrochlorothiazide (HCTZ) and valsartan/HCTZ at a tertiary care university hospital in Oman. ***Subjects and Methods:*** This was a retrospective observational study, where 232 patients' medical records were reviewed during a 3-month period, July to September 2010, at Sultan Qaboos University Hospital in Oman. BP readings of the previous 6 months were also retrieved from the electronic medical records. Analyses were conducted using univariate statistical techniques. ***Results:*** The mean age of the cohort was 58 ± 11 years (range: 21–88). Sixty-nine (30%) patients were on the irbesartan/HCTZ combination (150/12.5 mg) and 163 (70%) were on the valsartan/HCTZ combination. The patients on the valsartan/HCTZ combination were divided into two subgroups: 117 (72%) received 160/12.5 mg and 46 (28%) 80/12.5 mg. Diabetic patients (43/69, 62%, vs. 61/163, 37%, $p < 0.001$) and those with diabetic nephropathy (8/69, 12%, vs. 7/163, 4%, $p = 0.039$) were prescribed more often irbesartan/HCTZ than valsartan/HCTZ. In comparison to the valsartan/HCTZ cohort, the irbesartan/HCTZ group was associated with significant reductions in both systolic BP (SBP; –9 vs. –2 mm Hg; $p = 0.021$) and diastolic BP (DBP; –5 vs. 0 mm Hg; $p = 0.022$). BP reductions were noted more in diabetics than nondiabetics with the irbesartan/HCTZ patients associated with significant reductions in both SBP (–12 vs. 5.1 mm Hg; $p < 0.001$) and DBP (–6.4 vs. 1.9 mm Hg; $p = 0.001$). ***Conclusions:*** The irbesartan/HCTZ combination was associated with significant reductions in both SBP and DBP when compared with the valsartan/HCTZ combination. Specifically, the reductions were noted more in diabetics than nondiabetics.

Introduction

Hypertension is a chronic progressive cardiovascular disorder that affects about 26% of all adults worldwide [1]. Progression of hypertension leads to abnormalities in cardiac and vascular functions as well as structural damage to the heart, kidneys, brain, vasculature, and other organs, consequently leading to premature morbidity and death [2, 3]. Hypertension is diagnosed and treated at the threshold blood pressure (BP) levels of <140/90 and <130/85 mm-Hg in nondiabetic and diabetic patients, respectively [4]. Several classes of drugs are used to treat

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hypertension by targeting different aspects of its pathophysiology. Some of the drugs are used as monotherapy while others are used in combination. It is estimated that more than two thirds of hypertensive subjects are not controlled on one drug alone and will thus require two or more antihypertensive agents selected from different drug classes to provide optimum control [4].

Angiotensin II receptor blockers (ARBs) are an effective antihypertensive option with renal and cardioprotective effects coupled with lower adverse effect profile [5]. ARBs differ in pharmacodynamic and pharmacokinetic properties, which may translate into significant differences in their relative antihypertensive potency. ARBs are also available in fixed-dose combination with other antihypertensive drugs such as thiazide diuretics and calcium channel blockers. Valsartan is a potent ARB that has a good BP-lowering effect at doses of 80–320 mg [6]. It is also indicated for heart failure and postmyocardial infarction to reduce cardiovascular mortality [7]. Irbesartan is another ARB prescribed at doses from 75 to 300 mg. It is also approved for the treatment of hypertension. In some countries, irbesartan has been approved for the treatment of nephropathy in patients with hypertension and type 2 diabetes mellitus [8, 9]. There are currently only a few published studies [10, 11] on the comparison of irbesartan/hydrochlorothiazide (HCTZ) and valsartan/HCTZ combinations with respect to BP control. Therefore, the aim of this study was to compare the effectiveness of irbesartan/HCTZ and valsartan/HCTZ with respect to BP in patients with mild to moderate hypertension at Sultan Qaboos University Hospital, in Muscat, Oman.

Subjects and Methods

This was a retrospective observational study where the electronic medical records of 232 adult patients (≥18 years) who were prescribed irbesartan/HCTZ or valsartan/HCTZ and diagnosed with mild to moderate hypertension were reviewed in a 3-month period between July and September, 2010. The study took place at Sultan Qaboos University Hospital, which is a nearly 600-bed tertiary-care university hospital in Muscat, Oman. Each patient's BP readings were retrieved from the medical records for the previous 6 months prior to the index date. Patients were excluded if they did not have a diagnosis of mild to moderate hypertension. Furthermore, they also had to contribute at least two BP readings (one reading in the index period, July to September 2010, and the other BP reading in the preindex 6-month period). Patients were also excluded if they were not on the two study medications throughout the study period. Arterial BP was measured by a trained nurse using an oscillometric automatic BP monitor and by a physician using a calibrated standard sphygmomanometer of the appropriate cuff size. All BP measurements were taken after the patient had rested in a sitting position for 5 min.

Apart from the BP readings, the study also captured the following variables: age, weight, height, gender (male, female), nationality (Omani, non-Omani), other comorbidities (diabetes mellitus, dyslipidemia, ischemic heart disease, congestive heart failure, stroke, myocardial infarction, atrial fibrillation, anemia, obesity, diabetic nephropathy, diabetic retinopathy, and deep vein thrombosis), and other antihypertensive medications. Ethical approval for the study was obtained from the Ethics Review Committee of the College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman. The study was part of an MSc project for the second author (J.Q.), who did all the data collection while analyses were shared between all the authors.

Power Analysis

At least 6 months' follow-up on 177 patients were needed (118 on the valsartan group and 59 on the irbesartan group; 1:½ ratio, based on prevalence of prescribing) to have 80% power to detect a difference of 10 mm Hg of BP difference (systolic or diastolic) between the two cohorts at the 5% alpha (significance) level. Because of missing data, additional data were retrieved for 55 subjects for a total of 232 (study sample).

Statistical Analysis

Descriptive statistics were used to describe the data. For categorical variables, frequencies and percentages were reported. Differences between groups were analyzed using Pearson's χ^2 tests (or Fisher's exact tests for cells less than 5). For continuous variables, mean and standard deviation were used to present the data while analysis was performed using Student's t test or paired t test, wherever appropriate. An a priori two-tailed level of significance was set at the 0.05 level. Statistical analyses were conducted using STATA version 12.1 (STATA Corp., College Station, Tex., USA).

Results

The demographic characteristics of the study sample are summarized in table 1. Of the 232 patients whose data were obtained from medical records, 69 (30%) and 163 (70%) were on irbesartan/HCTZ and valsartan/HCTZ combinations, respectively. For those on irbesartan/HCTZ, the dose was 150/12.5 mg, while for those on the valsartan/HCTZ combination, 118 (72%) were on the 160/12.5 mg strength while the remaining 45 (28%) were on the lower strength, 80/12.5 mg. The overall mean age of the cohort was 58 ± 11 years (range: 21–88); 113 (49%) subjects receiving the irbesartan/HCTZ and valsartan/HCTZ combinations were males and 220 (95%) were Omanis. There were no significant differences in age (60 vs. 58 years; p = 0.134), gender (51 vs. 48% male; p = 0.689), Omani nationality (97 vs. 94%; p = 0.309), and weight (80 vs. 79 kg; p = 0.568) among the groups.

Table 1. Demographic characteristics of the study sample (n = 232)

Demographic characteristics	Irbesartan/ HCTZ (n = 69)	Valsartan/ HCTZ (n = 163)	All (n = 232)	p value
Mean age ± SD, years	60 ± 11	58 ± 11	58 ± 11	0.134
Male gender, n (%)	35 (51)	78 (48)	113 (49)	0.689
Omani national, n (%)	67 (97)	153 (94)	220 (95)	0.309
Mean weight ± SD, kg	80 ± 18	79 ± 18	79 ± 18	0.568

SD = Standard deviation.

Table 2. Clinical characteristics of the study cohort (n = 232)

Clinical characteristics	Irbesartan/ HCTZ (n = 69)	Valsartan/ HCTZ (n = 163)	All (n = 232)	p value
Diabetes mellitus	43 (62)	61 (37)	104 (45)	<0.001
Ischemic heart disease	14 (20)	24 (15)	38 (16)	0.295
Obesity	7 (10)	9 (6)	16 (7)	0.204
Nephropathy	8 (12)	7 (4)	15 (6.5)	0.039
Myocardial infarction	1 (1.5)	8 (4.9)	9 (3.9)	0.287
Chronic heart failure	1 (1.5)	4 (4.5)	5 (2.2)	1.000
Stroke	1 (1.5)	3 (1.8)	4 (1.7)	1.000
Atrial fibrillation	2 (2.9)	2 (1.2)	4 (1.7)	0.584
Anemia	1 (1.5)	2 (1.2)	3 (1.3)	1.000
Retinopathy	0 (0)	1 (0.6)	1 (0.4)	1.000
Deep vein thrombosis	0 (0)	1 (0.6)	1 (0.4)	1.000
	78	122	200	

Figures in parentheses indicate column percentages.
They might not add up to 100% because some patients had more than one comorbidity.

The clinical characteristics of the study cohort are summarized in table 2. Diabetic patients were prescribed irbesartan/HCTZ more than valsartan/HCTZ (62 vs. 37%; $p < 0.001$). The three other most frequent comorbid conditions included ischemic heart disease: 16%, obesity: 7%, and nephropathy: 6.5%. Patients with nephropathy were prescribed more irbesartan/HCTZ than valsartan/HCTZ (12 vs. 4%; p = 0.039). As shown in table 3, there were no significant differences in postindex BP measurements in either systolic BP (SBP; 144 vs. 142 mm Hg; p = 0.618) or diastolic BP (DBP; 76 vs. 77 mm Hg; p = 0.574) between the two cohorts. However, as compared to the valsartan/HCTZ cohort, the irbesartan/HCTZ group was associated with significant reductions in both SBP (–9 vs. –2 mm Hg; p = 0.021) and DBP (–5 vs. 0 mm Hg; p = 0.022). When stratified by diabetes mellitus, BP reductions were noted more in diabetics than nondiabetics. In diabetic patients, the irbesartan/HCTZ group was associated with more significant reductions in both SBP (–12 vs. 5.1 mm Hg; $p < 0.001$) and DBP (–6.4 vs. 1.9 mm Hg; p = 0.001). This significant difference was not apparent in nondiabetic patients ($p > 0.05$, table 3).

Discussion

This study showed that the irbesartan/HCTZ combination was associated with greater reductions in both SBP and DBP when compared with the valsartan/HCTZ combination. Specifically, the reductions were noted more in diabetics than nondiabetics. The study also showed that diabetic and hypertensive patients with nephropathy were more likely to be prescribed the irbesartan/HCTZ than valsartan/HCTZ combination.

It should be noted that patients were also on other antihypertensive medications (78% irbesartan/HCTZ vs. 69% valsartan/HCTZ). The cohort receiving the irbesartan/HCTZ combination had also more comorbid conditions compared to the valsartan/HCTZ cohort, especially diabetes mellitus and nephropathy, which could complicate the treatment of hypertension. However, the utilization of other antihypertensive medications was not significantly different between the two cohorts (78 vs. 69%; p = 0.147, table 4). It is known from major published clinical trials that ARBs are among the drugs of choice in hypertensive patients with diabetes, chronic renal failure or heart failure [4, 12]. Irbesartan/HCTZ fixed-dose combination is approved in the US for the treatment of patients who are not adequately controlled with irbesartan or HCTZ alone and in patients likely to require multiple drugs to reach target BP [12–14].

The efficacy of irbesartan and valsartan alone or in combination with HCTZ has been explored in several previous studies [10, 11, 15]. A recent post hoc analysis showed that the reduction in home SBP and DBP was numerically greater with irbesartan/HCTZ (150/12.5 mg) compared to valsartan/HCTZ (80/12.5 mg) for all subgroups (the difference in DBP was significant for all except the elderly, $p < 0.05$, and the difference in SBP was significant in the elderly and in men, p = 0.03) [14]. Another 8-week randomized study of 426 patients with mild to moderate hypertension showed that irbesartan 150 mg once daily was associated with superior 24-hour ambulatory BP control to valsartan 80 mg. In addition,

Table 3. Mean (±SD) BP differences of the study cohort (n = 232)

Blood pressure measurements	Irbesartan/HCTZ (n = 69)	Valsartan/HCTZ (n = 163)	All (n = 232)	p value
Pre SBP, mm Hg	153 ± 21	144 ± 19	146 ± 20	0.004
Pre DBP, mm Hg	81 ± 12	77 ± 14	78 ± 13	0.056
Post SBP, mm Hg	144 ± 20	142 ± 22	142 ± 22	0.618
Post DBP, mm Hg	76 ± 12	77 ± 13	77 ± 12	0.574
SBP post – SBP pre (difference in SBP)	–9 ± 21	–2 ± 23	–4 ± 23	0.021
DBP post – DBP pre (difference in DBP)	–5 ± 13	0 ± 13	–2 ± 13	0.022
Diabetic patients (n = 104)				
Difference in SBP	–12 ± 19	5.1 ± 25	–1.8 ± 24	<0.001
Difference in DBP	–6.4 ± 10	1.9 ± 13	–1.5 ± 13	0.001
Nondiabetic patients (n = 128)				
Difference in SBP	–5.0 ± 24	–5.9 ± 22	–5.7 ± 22	0.859
Difference in DBP	–2.0 ± 17	–1.6 ± 13	–1.7 ± 14	0.897

Pre = Preindex; post = postindex.

Table 4. Other antihypertensive medications utilized by the study subjects (n = 232)

	Irbesartan/HCTZ (n = 69)	Valsartan/HCTZ (n = 163)	All (n = 232)	p value
Only ARB with HCTZ	15 (22)	51 (31)	66 (28)	0.147
Combined with 1 drug (39%)				
BB	9 (13)	24 (15)	33 (14)	0.839
CCB	13 (19)	36 (22)	49 (21)	0.725
Diuretic	2 (2.9)	5 (3.1)	7 (3.0)	1.000
Vasodilator	0 (0)	1 (0.6)	1 (0.4)	1.000
Combined with 2 drugs (28%)				
CCB + BB	16 (23)	26 (16)	42 (18)	0.197
CCB + diuretic	4 (5.8)	3 (1.8)	7 (3.0)	0.201
BB + diuretic	2 (2.9)	6 (3.7)	8 (3.5)	1.000
BB + vasodilator	1 (1.5)	3 (1.8)	4 (1.7)	1.000
CCB + vasodilator	2 (2.9)	1 (0.6)	3 (1.3)	0.212
Vasodilator + diuretic	1 (1.5)	0 (0)	1 (0.4)	0.297
Combined with ≥3 drugs (5%)				
BB + diuretic + vasodilator	1 (1.5)	3 (1.8)	4 (1.7)	1.000
BB + CCB + diuretic	1 (1.5)	3 (1.8)	4 (1.7)	1.000
BB + CCB + vasodilator	1 (1.5)	1 (0.6)	2 (0.9)	0.507
BB + CCB + vasodilator + diuretic	1 (1.5)	0 (0)	1 (0.4)	1.000

Number of patients with percentages in parentheses.
BB = Beta-blocker; CCB = calcium channel blocker.

the proportion of patients who achieved normalized BP (DBP <90 mm Hg) was significantly greater in the irbesartan group compared to the valsartan group (53 vs. 38%; p = 0.004) [15]. Furthermore, the fixed-dose combination of irbesartan/HCTZ (150/12.5 mg) has been shown to achieve significantly superior BP lowering compared with valsartan/HCTZ (80/12.5 mg), as assessed by office BP measurements and home BP monitoring in the COSIMA (Comparative Study of Efficacy of Irbesartan/HCZ with Valsartan/HCZ Using Home Blood Pressure Monitoring in the Treatment of Mild to Moderate Hypertension) study [10]. The findings of the

current study confirmed the results of these earlier studies [10, 11, 15]. However, other studies [16, 17] have shown contrasting results. A study found no significant difference between irbesartan 150 mg and valsartan 80 mg in terms of efficacy of reducing SBP and DBP [16]. Another meta-analysis of randomized controlled trials for treatment of adult hypertension found that irbesartan 150 mg is less effective in reducing SBP and DBP than valsartan 160 mg, with differences in the mean change in BP of 3.56 mm Hg (95% CI: 0.77, 6.38) and 2.06 mm Hg (95% CI: 0.71, 3.45) [17]. In summary, published studies have demonstrated conflicting comparative efficacy of valsartan and irbesartan regarding BP control. These conflicting results could have been attributed to differences in methodologies including samples sizes and patient case-mix as well as differential doses of irbesartan and valsartan and combination therapies with HCTZ.

The limitations of this study include its retrospective nature. A significant proportion of patients had missing data on baseline BP readings and hence were excluded. This could also have affected the results. However, the fact that all patients that met the inclusion criteria over the 3-month period were captured without exception, this is likely to have minimized any biases.

Conclusions

The irbesartan/HCTZ combination was associated with significant reductions in BP when compared to the valsartan/HCTZ combination. The reductions were associated mainly in diabetics and patients with diabetic nephropathy. Thus, a significant implication of this study is that the irbesartan/HCTZ combination could be an appropriate therapy for patients with hypertension and diabetes.

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