Efficacy, Safety and Tolerability Of Valsartan Plus HCTZ in Patients With Essential Hypertension: A Multicentre Observational Study in Bangladesh

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Key word:
Valsartan, Hydrochlorothiazide, Hypertension.

Abstract:

Background: *Valsartan is an established drug for treatment of essential hypertension. It blocks the action of Angiotensin II irrespective of its sources. A large proportion of patients need additional treatment with two or more drugs of different pharmacological classes for achieving target blood pressure. Published evidence demonstrated synergistic effect of Thiazides with ARB. Co-administration of valsartan and Hydrochlorothiazide has the potential to reverse the untoward effect of each other. Current study aimed at evaluating the efficacy, safety and tolerability of Valsartan plus Hydrochlorothiazide combination, and thus validating the regimen in the treatment of essential hypertension in Bangladeshi population, a population significantly different from Caucasian population where most studies were done.*

Methods: *Current study is a prospective interventional study involving 404 Adult, patients, with Stage I (SBP 140-159 mmHg/DBP 90-99 mmHg) or Stage II (SBP≥160 mmHg/DBP ≥100 mmHg) essential hypertension or patients uncontrolled on current mono-therapy or other combination therapy. Valsartan plus HCTZ 80/12.5 mg once daily tablet were prescribed to continue till the following visit or for the remainder of the study. In case of inadequate control increment in dose was made on the following visit. Patients were assessed at baseline, at 4th weeks, 12th week and 24th week. One of the major outcome parameter set for the study was the percentage of participant having BP controlled that is a SBP <140 mmHg and DBP <90 mmHg or a reduction >10 mmHg for DBP and/or >20 mmHg SBP versus baseline values at 24 weeks. At final follow-up, in addition to repetition of the baseline measurements and examinations, data on Safety of the drug was collected by enquiring and recording all adverse events or serious adverse events. Global assessment of efficacy and tolerability of treatment was also done by both the physicians and patients on a 4-point scale.*

Result: *The percentage of participant having BP controlled at the end of the trial was 91%. Besides, Significant reduction in mean SBP and mean DBP was also evident (P<.001) through paired comparison from baseline to end of the study. Average reduction of 32.4 ± 19.5 mmHg was seen in systolic BP and 17.4 ± 9.3 mmHg in diastolic BP. Global assessment based on both physician and patients reported greater satisfaction with the efficacy of treatment modality. Total adverse event reported by only six (1.5%) participants. Of the six cases three of the adverse effect was reported at 3rd visit and another three were reported at 4th visit. Total five dropouts (1.24%) were reported of which 1 in 3rd visit and 4 in 4th visit. Among the dropout patient three were withdrawn from the study and two didn't attend the final follow-up. Global assessment of safety and tolerability based on both physician and patient's opinion reveals greater satisfaction level with the safety and tolerability of combination treatment.*

Conclusion: *The combination of valsartan and hydrochlorothiazide is an effective treatment for patients with essential hypertension. The combination is also effective in patients not responding to monotherapy with either agent. The drug is found to be well tolerated with minimal adverse event during the course of treatment.*

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Back ground:

The etio-pathogenisis of hypertension is multidimensional, various mechanisms and factors contribute hypertension, which includes genetic and environmental factors[1] that might be an answer to the failure or inadequacy of

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antihypertensive therapy. With prolonged use of ACE inhibitors the level of Angiotensin I is found to increase. The increased quantity of Angiotensin I then easily gets converted to Angiotensin II through the alternative pathways. Such formation of Angiotensin II through non-ACE pathways results in increasing Angiotensin II, even to the pre-treatment or basal level. In simple words ACE inhibitors may not maintain their initial efficacy with chronic use.

The use of Angiotensin II receptor blockers for first-line therapy is well documented.[1,2] Particularly valsartan has been shown to be an effective alternative to other antihypertensive drugs in the treatment of essential hypertension.[3] Valsartan being an Angiotensin II receptor antagonist works at the receptor level and blocks effects of Angiotensin II. Valsartan blocks the action of Angiotensin II formed irrespective of its source. Despite the clinical efficiency of mono-therapy in treating hypertension, approximately seventy percent patients need additional treatment requiring concomitant therapy with two or more drugs from different classes. Combination therapy has the potential of higher antihypertensive efficacy in lower doses and thus low incidence of adverse effects is expected. Evidence increasingly points towards combination therapy as a necessary treatment regimen to achieve control in the majority of hypertensive patients. The combination of an ARB with low dose HCTZ does not produce more side effects than placebo and provides additional powerful BP lowering that is significantly greater than that of either drug alone.[4]

Several clinical trials in different setting have demonstrated greater efficacy of combination of valsartan 80mg or 160mg with hydrochlorothiazide 12.5mg or 25mg over mono-therapy by one of the drugs alone.[1,2,3,4] Moreover, the regimen has been shown as more effective at reducing BP refractory to mono-therapy with one of the components. Besides, the antihypertensive effects are maintained in long-term therapy.[5] Although the efficacy and safety of the valsartan/ hydrochlorothiazide combination as sequential therapy is well established, the use of the combination as first-line treatment is not yet well established. Gavras and Rosenthal[6] examined the rationale for combining drugs from different classes that have synergistic or additive effects and properties that might offset one another's adverse hemodynamic and/or metabolic reactions. They suggested circumstances in which the initiation of therapy with a fixed two-drug combination might be preferable to the usual practice of starting with mono-therapy followed by upward titration and addition of other agents. They end with the intriguing and provocative notion of the future "polypill," a fixed combination of agents addressing various mechanism of hypertension as well as other coexisting common risk factors in both high-risk patients with conditions requiring poly-pharmacy.

The safety profile and efficacy was not assessed in Bangladeshi population, a population significantly different from Caucasian, Negrito and other racial variations. The aim of this study was to determine the overall effect of a treatment regimen in terms of reduction in mean systolic BP and mean diastolic BP with treatment at 24 weeks, and to gauge the efficacy and tolerability of Valsartan in combination with HCTZ at 24 weeks in Bangladeshi population and in its registered indication in treating patients with essential hypertension.

Methodology

Patients and materials

Current effort is an open-label, multicenter, prospective study conducted to assess safety and efficacy of fixed dose combination of Valsartan and Hydrochlorothiazide in Bangladeshi population. A total of 404 Adult, male or female naïve patients, of age ranging 18 to 65 years, with Stage I (SBP 140-159 mmHg/DBP 90-99 mmHg) or Stage II (SBP≥160 mmHg/DBP ≥100 mmHg) essential hypertension or patients uncontrolled on current mono-therapy or other combination therapy and were eligible to receive prescription for Valsartan and Hydrochlorothiazide as determined by their physician were recruited. Patients with severe medical condition, known hypersensitivity to any of the components in the formulation and women who were pregnant or breastfeeding were excluded.

After thorough baseline evaluation valsartan plus HCTZ 80/12.5 mg tablet were prescribed to take orally, once daily to continue till the following visit or for the remainder of the study, based on the blood pressure control. In case of inadequate

control increment in dose was made to 160/12.5 mg or 160/25 mg once daily. To maintain similarity in intervention all the patients were prescribed the investigational drug of same brand (Co-diovan® tablet containing valsartan and HCTZ of required dose). To avoid contamination of results, Patients having concomitant therapy with other anti-hypertensive or drugs with the potential of confounding effect in judgment of the treating physician were dropped. If any concomitant therapy was allowed, documentation was ensured.

Outcome assessment

Besides pre-enrollment assessment the patient's were assessed at 4th weeks, 12th week and 24th week. Efficacy of treatment was primarily assessed based on percentage of subjects having SBP<140 mmHg and/or DBP<90 mmHg or a reduction >10 mmHg for DBP and/or >20 mmHg SBP versus baseline values at 24 weeks. Besides, Reduction in mean SBP and mean DBP was also assessed as efficacy parameter. Global assessment of efficacy and tolerability of treatment was done by both the physicians and patients on a 4-point scale. Additionally safety and tolerability assessments focused on monitoring and recording of all adverse events and serious adverse events. Any untoward event in a patient or revealed through clinical investigation found in patient during the study period which does not necessarily have a causal relationship with given treatment was considered as an adverse event. Any untoward occurrence that results in death, life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, were considered as serious adverse event. Participating physicians were assigned to record adverse events at the follow-up visits or when they are notified. The study was approved by the institutional review board and was conducted maintaining confidentiality.

Statistical analysis

To protect the confidentiality of data and to preserve patient anonymity, de-identified data were proceeded for analysis through assigning a unique identifier number. Demographic and baseline characteristics were described by descriptive summary statistics. The evaluation of the efficacy was done based on the relative frequency of patients with a controlled systolic and diastolic pressure. The efficacy analyses of reduction in BP were performed by assessing mean of paired difference between baseline and final visit with generation of P value and confidence intervals. For determining control rate relative frequency of patient achieved target BP was generated. The safety and tolerability evaluation was performed based on the relative frequency. Four point global assessment data of safety and tolerability were analyzed through generating descriptive statistics. The data were analyzed using SPSS® 16.

Results:

a. Patient characteristics:

Table-I

Socio demographic characteristics (n=404)

	Frequency	Percent
Age		
< 40 years	26	6.4
40 - 49 years	118	29.2
50 - 59 years	154	38.1
≥60 years	106	26.2
Sex		
Male	274	67.8
Female	130	32.2
BMI		
< 18.5	12	3.0
18.5 - 25.0	170	42.1
> 25.0	222	55.0
Currently on medication		
No	277	68.6
Yes	127	31.4

Out of 404 Adult hypertensive patients 6.4% were aged less than 40 years, 29.2% were aged between 40 – 49 years, 38.1% were aged between 50 – 59 years and 26.2% were aged above 60 years. Mean age of the patient was 52.62 ±8.30 years. Among them male to female ratio was around 2:1. Three percent of them had BMI < 18.5, 42.1% had BMI between 18.5 to 25 and 55% had BMI over 25. Among the patient around two third were on any sort of medication and 31.4% were naïve.

b. Treatment profile

Table-II

Treatment profile

Treatment profile	Visit 2 (N=404)	Visit 3 (N=401)	Visit 4 (N=399)
Change in medication	16 (4.0)	14 (3.5)	5 (1.2)
New concomitant started	6 (1.5)	8 (2.0)	4 (1.0)
Adverse event	0 (0.0)	3 (.7)	3 (.8)
Drop out	0 (0.0)	1 (.2)	4 (0.96)

At the end of the study total adverse event reported was 6 (1.5%) and total dropout was 5 (1.24%)

At the commencement of the study 97.3% were prescribed with Valsartan 80mg with HCTZ 12.5 mg and 2.7% were given with Valsartan 160 mg with HCTZ 12.5mg. At 2nd visit 5.4% were given with Valsartan 160 mg with HCTZ 12.5mg and 8.7% were given with Valsartan 160 mg with HCTZ 25 mg. At 4th visit patient requiring Valsartan 160 mg with HCTZ 25mg rose to 9.3%.

Among the study subjects medication were changed at 2nd visit in 4%. The percentage was 3.5% and 1.2% in next two visits. New concomitant treatment was started in 1.5% cases at 2nd visit and 2% in 3rd visit and in 1% at 4th visit. Adverse event was reported in three cases (0.7%) in 3rd visit and in another three cases (.8%) at 4th visit. Total five dropouts (1.24%) were reported of which 1 in 3rd visit and 4 in 4th visit. Among the dropout patient three were withdrawn from the study and two didn't attend the final follow-up.

c. Assessment of BP reduction

A clearly evident decline is evident in mean Systolic BP, diastolic BP and heart rate (Figure 1). The fall of mean Systolic BP is steeper than that of Diastolic BP. Average Heart rate dropped from 77.4/m to 74.2 at the end of the study.

Change in BP and Heart rate was assessed at the end of the treatment in comparison to baseline parameters through paired t test. Average reduction of 32.4 ± 19.5 mmHg was seen in systolic BP, 17.4 ± 9.3 mmHg in diastolic BP and 3.1 ± 6.0/ minute in heart rate. The reduction was highly significant in both systolic BP and diastolic BP and heart rate as well (P<.001).

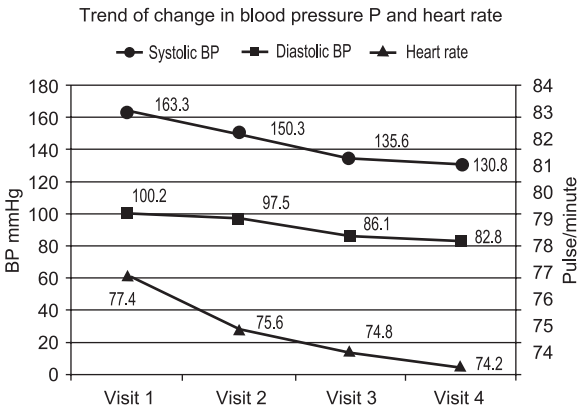

Fig.-1: *Trend of blood pressure reduction over the study period.*

d. Global assessment of safety and efficacy

Efficacy of the treatment was assessed based primarily on the opinion of the patient and physician concerned on four point scale. Around 38% of the physician rated the efficacy as excellent, around 42% rated as very good and 19.3% rated as good. Regarding patient's opinion around 30% rated the efficacy as excellent, around 48% rated as very good, around 22% rated as good and only 0.3% (1) rated as poor.

Tolerability of the treatment was also assessed based on the opinion of the patient and physician concerned on four point scale. Around 46% of the physician rated the tolerability as excellent, around 36% rated as very good and 18.5% rated as good. Regarding patient's opinion around 42% rated the tolerability as excellent, around 37% rated as very good, around 21% rated as good and only 0.3% (1) rated as poor.

Table-III

Reduction of BP after treatment

Variables	Assessment time		Paired mean difference		
	Before treatment	After treatment	Difference	t value	P value
SBP(N=399)	163.2±19.9	130.8 ± 9.7	32.4 ± 19.5	33.173	.001*
DBP(N=399)	100.2 ± 9.7	82.8 ± 7.2	17.4 ± 9.3	37.338	.001*
Heart rate (N=399)	77.3 ± 6.9	74.2 ± 5.4	3.1 ± 6.0	10.336	.001*

Percentage control at the end of the trial 91% (363)

Table-IV

Global assessment of efficacy

Assessment of efficacy	Physician's assessment		Patient's assessment	
	Frequency	Percent	Frequency	Percent
Excellent	153	38.3	120	30.1
Very Good	169	42.4	191	47.9
Good	77	19.3	87	21.8
Poor	0	0.00	1	.3
Total	399	100.0	399	100.0

Table-V

Global assessment of tolerability

Assessment of tolerability	Physician's assessment		Patient's assessment	
	Frequency	Percent	Frequency	Percent
Excellent	182	45.6	166	41.6
Very Good	143	35.8	148	37.1
Good	74	18.5	84	21.1
Poor	0	0.00	1	.3
Total	399	100.0	399	100.0

Discussion:

The use of ARB II for first-line therapy for essential hypertension is well documented.[2] Valsartan, an angiotensin II receptor blocker with selectivity for the type I receptor subtype, is an established drug for the treatment of essential hypertension. It blocks the action of Angiotensin II irrespective of its origin[3]. Effective BP control is often not achieved with mono-therapy. Crossover rotation trial of mono-therapy by anti-hypertensives, demonstrated a normalization rates of less than forty percent.[11] The HOT (Hypertension Optimal Treatment) study showed such response in only every third patients with mono-therapy. Approximately seventy percent of patients need additional treatment requiring concomitant therapy with two or more drugs of different pharmacological classes.[12] Physicians have to resort to effective combinations comprise antihypertensive agents with different primary actions, thus eliciting an additive hypertensive effect.

Evidence increasingly points towards combination therapy as a necessary treatment regimen to achieve control in the majority of hypertensive patients. Recent guidelines have confirmed the value of combination therapy in first-line therapy.[13,14] Besides, combination therapy has the potential of higher antihypertensive efficacy in lower doses and thus low incidence of adverse effects is expected. Trials demonstrated synergistic effect of thiazide with ARB.[5,6] Thiazide diuretics such as hydrochlorothiazide have been used in antihypertensive therapy since the advent of chlorothiazide in 1957, often in combination with other antihypertensive.[15] Thiazide diuretics primarily acts in the distal convoluted tubules through inhibition of sodium and chloride ion, perhaps by competing for chloride site affecting mechanisms of electrolyte re-absorption; directly increasing excretion of sodium and chloride ion in approximately the same amount, also indirectly, supporting diuretic action reducing plasma volume, with consequent increase in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss and decreases in serum potassium. The renin-aldosterone link is mediated by Angiotensin II. Hence co-administration of an Angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.[15]

Current study focused on the use of the combination of valsartan and hydrochlorothiazide in the treatment of essential hypertension with

documented endpoint benefit in Bangladeshi population. The study only restricted to naïve patients with Stage I or Stage II essential hypertension or patients uncontrolled on current mono-therapy or other combination therapy. The study avoided comparison with placebo group as the efficacy of the fixed dose combination of the two drugs under study has already been documented in numerous clinical trials in different population, The primary goal of our current effort is to validate the treatment modality in Bangladeshi population, however a prospective setting was employed and all patients were assessed baseline, at 4th weeks, 12th week and 24th week.

At the beginning 97.3% were given with Valsartan 80mg with HCTZ 12.5 mg and the rest were given with Valsartan 160 mg with HCTZ 12.5mg. At 2nd visit the proportion of patient required Valsartan 160 mg with HCTZ 12.5mg rose to 5.4% and additionally 8.7% were given with Valsartan 160 mg with HCTZ 25 mg. At 3rd visit the proportion of patient requiring Valsartan 160 mg with HCTZ 25mg rose to 9.3%. Increment in dose, although minimum, demonstrates a relative under response or non response with the initial therapy, however leaves the ground for upward titration for achieving the target BP. These allows physician to minimize untoward effect exerted by administration of higher dose of single drug. Article published in 'Current Hypertension Reports' suggested combining drugs with different mode of action that have synergistic or additive effects to neutralize or at least to minimize adverse hemodynamic or metabolic effect of each other. They proposed initiation of therapy with drug combinations followed by upward titration of one of the agents if required.[10]

One of the major outcome parameter set for the study was the percentage of participant having BP controlled that is a SBP <140 mmHg and DBP <90 mmHg or a reduction >10 mmHg for DBP and/or >20 mmHg SBP versus baseline values at 24 weeks. Percentage control at the end of the trial was 91%, which is quite high for response of a treatment regimen. Besides, reduction in mean SBP and mean DBP was also assessed as efficacy parameter. Reduction in mean Systolic BP, diastolic BP and heart rate (P<.001) was evident through paired comparison from baseline to end of the study. Average reduction of 32.4 ± 19.5 mmHg was seen in systolic BP and 17.4 ± 9.3 mmHg in diastolic BP.

Efficacy of the treatment was also assessed based on the opinion of the patient and physician concerned on four point assessment scale. A potential limitation embedded in the design was that for safety data we had to depend on the turnout of patient at final follow-up. However, in the current study out of 404 participants total attrition was only five (1.24%). Among the dropouts three withdrew from the study and only two didn't attend the final follow-up. The figure was not bigger enough to impede the generalizability of the study finding. Around 39% of the physician rated the efficacy as excellent, around 42% rated as very good and 19.3% rated as good. Regarding patient's opinion around 30% rated the efficacy as excellent, around 48% rated as very good, around 22% rated as good and only 0.3% (1) rated as poor.

According to the data of current study a large proportion of patients benefit from the combination of Valsartan and hydrochlorothiazide. Considering the overall treatment effect, as many as 91% of patients showed a response to the combination. All the three parameter used for efficacy assessment namely, mean BP reduction, Percentage control and satisfaction by both physician and patients confirms the efficacy of combination of valsartan and HCTZ as an effective antihypertensive. A series of clinical trials have demonstrated superior efficacy of fixed dose combination of valsartan 80mg or 160mg with hydrochlorothiazide 12.5mg or 25mg over mono-therapy by either drug.[7,8,9] Moreover, the regimen has been shown as more effective at reducing BP refractory to monotherapy with one of the components. Besides, the antihypertensive effects are maintained in long-term therapy.[16,17] VAST study[18] compared Valsartan and Hydrochlorothiazide combination with amlodipine in reducing systolic blood pressure (SBP) in patients with moderate (stage II) hypertension. And they confirmed superior antihypertensive effects with the fixed-dose combinations of valsartan and HCTZ compared with amlodipine, with significantly lower rates of treatment-related adverse events and possible beneficial effects on vascular markers.

Safety and tolerability assessments focused on monitoring and recording of all adverse events and

serious adverse events. At final follow-up, in addition to repetition of the baseline measurements and examinations, data on Safety of the drug was collected by inquiring and recording all adverse events or serious adverse events. Any untoward event in a patient or reveled through clinical investigation found in patient during the study period which may or may not have a causal relationship with given treatment was recorded and reported by participating physician. Total adverse event reported by only six (1.5%) participants. Of the six cases three of the adverse effect was reported at 3rd visit and another three were reported at 4th visit.

An important aspect of this study is the good safety profile and tolerability of valsartan/ hydrochlorothiazide combinations. Overall incidence of adverse event and the incidence of drug-related adverse events were very low, which supports data from previous trials.[5,1] The overall incidence of adverse events associated with valsartan/hydrochlorothiazide reported in clinical trial by Perrinel et al, was similar to that with placebo and lower than that with amlodipine.[2] According to study by malacco the valsartan/HCTZ combination was better tolerated than amlodipine, which was associated with a higher frequency of ankle edema and combination of valsartan 160 mg and HCTZ 12.5 mg provides more sustained and homogeneous control of blood pressure than does amlodipine 10 mg in high-risk hypertensive patients, without producing reflex sympathetic activation.[21]

Tolerability of the treatment was also assessed based on the opinion of the patient and physician concerned on four point scale. Around 46% of the physician rated the efficacy as excellent, around 36% rated as very good and 18.5% rated as good. Regarding patient's opinion around 42% rated the tolerability as excellent, around 37% rated as very good, around 21% rated as good and only 0.3% (1) rated as poor.

A review[22] of pharmacology, therapeutic efficacy and place in the management of hypertension demonstrated that combination of valsartan and hydrochlorothiazide is an effective treatment for patients with hypertension. Clinical trials have demonstrated that the combination is more effective than either drug alone, and is effective in patients not responding to monotherapy with either agent. Furthermore, according to their review, the adverse event profile of valsartan/ hydrochlorothiazide is similar to that of placebo. Unless there are compelling or specific indications for other drugs, their data support the use of valsartan/hydrochlorothiazide when patients are unresponsive to monotherapy with either agent. Results from clinical trials evaluating the effects of valsartan/hydrochlorothiazide on cardiovascular morbidity and mortality would help to further define the role of the combination in the management of hypertension.

Our study substantiate similar standpoint to the safety and efficacy of combination therapy with Valsartan and HCTZ reveled in other population. Current study upholds the use of the two drugs together in fixed dose combination as an effective and safe antihypertensive treatment modality. Current study is a prospective observational study, neither randomized nor blinded, which to some extent limits generalizability of the findings, however, the intent of the researcher was to assess the safety and efficacy of the treatment modality in our population which was already recommended by large, well designed and well powered study studies done elsewhere in wide range of population and patient settings. Further investigation could preferably be done with better study design for even stronger evidences.

In conclusion, 24 week treatment with the combination of valsartan and hydrochlorothiazide is an effective treatment for patients with essential hypertension. The combination is also effective in patients not responding to monotherapy with either agent. The drug is found to be well tolerated with minimal adverse event during the course of treatment.

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