International Journal of Medicine and Nanotechnology
© Mednano Publications
An International Peer Review Journal

e ISSN: 2394-4269

Original Article

TRIPLE COMBINATION THEAPY WITH AMLODINE, VALSARTAN AND HYDROCHLOROTHIAZIDE vs DUAL COMBINATION THERAPY WITH AMLODIPINE AND HYDRCHLOROTHIAZIDE FOR STAGE 2 HYPERTENSIVE PATIENTS

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Abstract:
Blood pressure is expressed by two measurements, the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively.[2] Normal blood pressure at rest is within the range of 100–140 millimeters mercury (mmHg) systolic and 60–90 mmHg diastolic.[7] High blood pressure is present if the resting blood pressure is persistently at or above 140/90 mmHg for most adults. Different numbers apply to children. Ambulatory blood pressure monitoring over a 24-hour period appears more accurate than office best blood pressure measurement. to assess the benefits of the triple combination with Aml/Val+HCTZ compared with Aml+HCTZ dual therapy in patients with stage 2 hypertension.Evaluated the efficacy and safety of triple therapy with amlodipine/valsartan+hydrochlorothiazide (Aml/Val+HCTZ) vs dual therapy with Aml+HCTZ in stage 2 hypertensive patients. Changes in msSBP and msDBP at week 8 were analyzed using analysis of covariance model with treatment and region as factors and baseline BP (week 0 or week 4 depending on analysis) as a covariate. The results were presented as least squares mean difference between the treatment groups with 95% confidence interval and *P* value. This study provides relevant information as it follows the clinical practice of prescribing a third antihypertensive agent in a step-wise manner to initial dual therapy depending on BP levels of the patient. The present analyses, however, have certain limitations: 1) this was a *post hoc* analysis of a study not designed to evaluate the efficacy of triple therapy vs dual therapy; 2) patients were not randomized to receive Aml/Val/HCTZ and Aml/HCTZ; and 3) the duration of the treatment with triple therapy was four weeks. In conclusion, triple combination therapy with Aml/Val/HCTZ provides significantly greater BP reductions and is well tolerated compared with Aml/HCTZ dual therapy in stage 2 hypertension and can provide additional benefits in patients who require more than two agents to reach their target BP.

1. INTRODUCTION

Hypertension (HTN or HT), also known as high blood pressure (HBP), is a long term medical condition in which the blood pressure in the arteries is persistently elevated.[1] High blood pressure usually does not cause symptoms.[2] Long term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease.[3][4]

High blood pressure is classified as either primary (essential) high blood pressure or secondary high blood pressure.[5] About 90–95% of cases are primary, defined as high blood pressure due to nonspecific lifestyle and genetic factors.[5][6] Lifestyle factors that increase the risk include excess salt, excess body weight, smoking, and alcohol.[2][5] The remaining 5–10% of cases are categorized as secondary high blood pressure, defined as high blood pressure due to an identifiable cause, such as chronic kidney disease, narrowing of the kidney arteries, an endocrine disorder, or the use of birth control pills.[5]

Blood pressure is expressed by two measurements,
the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively.[2] Normal blood pressure at rest is within the range of 100–140 millimeters mercury (mmHg) systolic and 60–90 mmHg diastolic.[7] High blood pressure is present if the resting blood pressure is persistently at or above 140/90 mmHg for most adults.[5] Different numbers apply to children.[8] Ambulatory blood pressure monitoring over a 24-hour period appears more accurate than office best blood pressure measurement.[1][5]

Lifestyle changes and medications can lower blood pressure and decrease the risk of health complications.[9] Lifestyle changes include weight loss, decreased salt intake, physical exercise, and a healthy diet.[5] If lifestyle changes are not sufficient then blood pressure medications are used.[9] Up to three medications can control blood pressure in 90% of people.[5]The treatment of moderately high arterial blood pressure (defined as >160/100 mmHg) with medications is associated with an improved life expectancy.[10] The effect of treatment of blood pressure between 140/90 mmHg and 160/100 mmHg is less clear, with some reviews finding benefit[11][12] and others finding a lack of evidence for benefit.[13] High blood pressure affects between 16 and 37% of the population globally.[5] In 2010 hypertension was believed to have been a factor in 18% (9.4 million) deaths

SIGNS AND SYMPTOMS:

Hypertension is rarely accompanied by symptoms, and its identification is usually through screening, or when seeking healthcare for an unrelated problem. Some with high blood pressure report headaches (particularly at the back of the head and in the morning), as well as lightheadedness, vertigo, tinnitus (buzzing or hissing in the ears), altered vision or fainting episodes.[15] These symptoms, however, might be related to associated anxiety rather than the high blood pressure itself.[16]

On physical examination, hypertension may be associated with the presence of changes in the optic fundus seen by ophthalmoscopy.[17] The severity of the changes typical of hypertensive retinopathy is graded from I–IV; grades I and II may be difficult to differentiate.[17] The severity of the retinopathy correlates roughly with the duration or the severity of the hypertension

Secondary hypertension[edit]
Main article: Secondary hypertension

Hypertension with certain specific additional signs and symptoms may suggest secondary hypertension, i.e. hypertension due to an identifiable cause. For example, Cushing's syndrome frequently causes truncal obesity, glucose intolerance, moon face, a hump of fat behind the neck/shoulder, and purple abdominal stretch
marks.[18] Hyperthyroidism frequently causes weight loss with increased appetite, fast heart rate, bulging eyes, and tremor. Renal artery stenosis (RAS) may be associated with a localized abdominal bruit to the left or right of the midline (unilateral RAS), or in both locations (bilateral RAS). Coarctation of the aorta frequently causes a decreased blood pressure in the lower extremities relative to the arms, or delayed or absent femoral arterial pulses. Pheochromocytoma may cause abrupt ("paroxysmal") episodes of hypertension accompanied by headache, palpitations, pale appearance, and excessive sweating.[18]

Hypertensive crisis[edit]
Main article: Hypertensive crisis

Severely elevated blood pressure (equal to or greater than a systolic 180 or diastolic of 110) is

referred to as a hypertensive crisis. Hypertensive crisis is categorized as either hypertensive urgency or hypertensive emergency, according to the absence or presence of end organ damage, respectively.[19][20]

In hypertensive urgency, there is no evidence of end organ damage resulting from the elevated blood pressure. In these cases, oral medications are used to lower the BP gradually over 24 to 48 hours.[21]

In hypertensive emergency, there is evidence of direct damage to one or more organs.[22][23] The most affected organs include the brain, kidney, heart and lungs, producing symptoms which may include confusion, drowsiness, chest pain and breathlessness.[21] In hypertensive emergency, the blood pressure must be reduced more rapidly to stop ongoing organ damage,[21] however, there is a lack of randomised controlled trial evidence for this approach.[23]

to assess the benefits of the triple combination with Aml/Val+HCTZ compared with Aml+HCTZ dual therapy in patients with stage 2 hypertension. Evaluated the efficacy of triple therapy with amlodipine/valsartan+hydrochlorothiazide (Aml/Val+HCTZ) vs dual therapy with Aml+HCTZ Evaluated the Safety and tolerability of triple therapy with amlodipine/valsartan+hydrochlorothiazide (Aml/Val+HCTZ) vs dual therapy with Aml+HCTZ. MATERIALS AND METHODS:

This was a *post hoc* analysis of an eight-week, multicenter (75 centers in Europe and the United States), randomized, double-blind, parallel-group study. The methods are described in detail by Destro et al.17 After a three to seven-day washout period, all eligible patients (stage 2 hypertension [msSBP ≥ 160 mmHg and < 200 mmHg]) were randomized at baseline (week 0) to receive either Aml/Val 5/160 mg or Aml 5 mg for two weeks. After two weeks, the dose of Aml was force-titrated from 5 mg to 10 mg in both treatment arms. HCTZ 12.5 mg was added to both treatment groups at week 4 (open-label), if the patient had not reached the pre-specified protocol criteria of msSBP < 130 mmHg.

All patients included in this study were aged ≥18 years. Patients were excluded at screening if msSBP was <140 mmHg while receiving more than three antihypertensive medications, or if msSBP was ≥140 mmHg and <180 mmHg while receiving more than two antihypertensive treatments, or if msSBP was ≥180 mmHg while receiving more than one antihypertensive medication. Patients with hepatic or renal impairment, secondary hypertension, clinically significant cerebrovascular and cardiovascular disease, type 1 diabetes, and inadequately controlled type 2 diabetes were also excluded.

Efficacy and safety assessments

Demographics and baseline characteristics of patients requiring HCTZ and those not requiring HCTZ at week 4 were summarized. For the efficacy and safety analyses, only the subgroup of patients that required addition of HCTZ at week 4 were evaluated. The efficacy variables were change in msSBP and mean sitting diastolic blood pressure (msDBP) from baseline to week 8, week 4 to week 8, and overall BP control rate (<140/90 mmHg) at week 8. Because HCTZ was to be added if msSBP was ≥ 130 mmHg, patients included in the efficacy analyses may have an msSBP <140 mmHg at week 4. To eliminate bias in assessing the effect of add-on HCTZ therapy on BP control at week 8, patients with BP <140/90 mmHg at week 4 were excluded from the control rate analysis. Subgroup analyses were also performed according to the severity of hypertension (msSBP ≥ 180 mmHg at baseline), diabetic status, age group (≥65 years), race (Caucasians and Non-Caucasians), and body mass index (BMI) ≥ 30 kg/m^2.

At each visit, sitting BP were measured three times at two to three-min intervals using an Omron BP monitor (Omron Healthcare, Milton Keynes, UK) in accordance with the British Hypertension Society guidelines.18 BP readings were made by the same clinician whenever possible, at drug trough (ie, 24 ± 3 h post-dose). Safety assessments for this analysis consisted of a summary of AEs during week 4 to week 8 of treatment.

Statistical analysis

Data gathered in this *post hoc* analysis was summarized with respect to demographic, efficacy, and safety variables. All efficacy analyses were conducted for the intent-to-treat population (randomized patients with a baseline and at least one post-baseline efficacy assessment).

Changes in msSBP and msDBP at week 8 were analyzed using analysis of covariance model with treatment and region as factors and baseline BP (week 0 or week 4 depending on analysis) as a covariate. The results were presented as least squares mean difference between the treatment groups with 95% confidence interval and *P* value. The proportion of patients achieving BP control was analyzed using a logistic regression model, with treatment as factor and baseline BP as a covariate. Summary statistics were performed for further subgroups by age, gender, BMI, and severe SBP at baseline.

RESULTS AND DISCUSSION:

Of the patients randomized to Aml/Val (N = 322) and Aml (N = 324) treatment arms, 136 (42%) and 208 (64%), respectively, required add-on HCTZ, of whom 133 (98%) and 200 (96%) completed the study.

Demographic and baseline characteristics of patients requiring add-on HCTZ and those not requiring add-on HCTZ at week 4 are presented in Table 1. Compared to patients who did not receive add-on HCTZ, a greater percentage of patients requiring add-on HCTZ had diabetes (6.6% vs 14.8%) and severe hypertension at baseline (13.6% vs 18.0%). The baseline msBP of patients requiring add-on HCTZ (Aml/Val+HCTZ: 171.5/96.4 mmHg, Aml+HCTZ: 171.5/95.0 mmHg) was numerically higher compared with patients who did not require add-on therapy (Aml/Val: 169.3/95.1 mmHg, Aml: 169.8/94.1 mmHg). Within the patients who received add-on HCTZ, demographic and baseline characteristics were comparable between the two treatment groups.

Characteristics	**Patients not requiring HCTZ**		**Patients requiring add-on HCTZ**	
	Aml/Val (N = 186)	**Aml (N = 116)**	**Aml/Val HCTZ (N = 136)**	**Aml HCTZ (N = 208)**
Age ± SD (years)	57.5 ± 10.6	57.3 ± 10.8	58.8 ± 9.8	58.5 ± 10.2
Age category, n (%)				
<65 years	137 (73.7)	85 (73.3)	98 (72.1)	149 (71.6)
≥65 years	49 (26.3)	31 (26.7)	38 (27.9)	59 (28.4)
Gender, n (%)				
Male	94 (50.5)	51 (44.0)	71 (52.2)	108 (51.9)
Race, n (%)				
Caucasians	159 (85.5)	93 (80.2)	102 (75.0)	174 (83.7)
Blacks	6 (3.2)	2 (1.7)	15 (11.0)	10 (4.8)
Others	21 (11.3)	21 (18.1)	19 (13.9)	24 (11.6)
msSBP ± SD, mmHg	169.3 ± 8.6	169.8 ± 9.1	171.5 ± 9.2	171.5 ± 8.1
msDBP ± SD, mmHg	95.1 ± 9.5	94.1 ± 10.9	96.4 ± 10.4	95.0 ± 10.2
Hypertension severity at baseline, n (%)	22 (11.8)	19 (16.4)	25 (18.4)	37 (17.8)
≥180 mmHg				
Diabetes; n (%)	13 (7.0)	7 (6.0)	22 (16.2)	29 (13.9)
BMI, Mean ± SD	28.9 ± 4.9	29.7 ± 5.9	31.1 ± 5.9	30.7 ± 5.6

The msSBP and msDBP of patients with week 4 HCTZ add-on therapy is plotted over time in Figure 1. For each post-baseline (week 0) measurement, patients belonging to Aml/Val+HCTZ triple therapy group achieved higher BP reduction than those in Aml+HCTZ dual therapy group, with an msBP of 141.2/82.2 mmHg vs 147.7/87.0 mmHg at week 8. An additional BP-lowering benefit was observed after the week 4 HCTZ add-on in both treatment groups. However, the incremental reduction from week 4 to week 8 was significantly greater with HCTZ added to Aml/Val compared with HCTZ added to Aml (6.9/3.5 vs 3.1/1.0 mmHg, $P < 0.01$)

N	**msSBP**		**MsDBP**		
	LSM change (SEM	**Difference (95% CI)**	**LSM change (SEM**	**Difference (95% CI)**	

	)		)		
From baseline to week 8					
Aml/Val+HCTZ	133	−30.5 (1.1)	−6.1 (−8.6, −3.6)	−13.8 (0.7)	−5.5 (−7.1, −3.9)
Aml+HCTZ	206	−24.3 (0.9)	*P* < 0.0001	−8.3 (0.6)	*P* < 0.0001
From week 4 to week 8					
Aml/Val+HCTZ	133	−6.9 (0.9)	−3.8 (−6.1, −1.5)	−3.5 (0.6)	−2.6 (−3.9, −1.1)
Aml+HCTZ	206	−3.1 (0.8)	*P* = 0.0012	−1.0 (0.5)	*P* = 0.0004

The overall reduction from baseline to week 8 was also significantly greater in the Aml/Val+HCTZ triple combination compared to Aml+HCTZ therapy (30.5/13.8 vs 24.3/8.3 mmHg, *P* < 0.0001) (Table 2).

In patients not adequately controlled (BP >140/90 mmHg) at week 4 on their existing medication, HCTZ 12.5 mg add-on for an additional four weeks facilitated attaining msBP < 140/90 mmHg in a higher proportion of patients previously on Aml/Val (37.7%) than Aml monotherapy (15.4%).

Subgroups

Similarly greater reductions in msBP with Aml/Val+HCTZ triple therapy were observed in all the subgroups by severity of hypertension, diabetic status, age group, race, and BMI, compared with the reductions with Aml+HCTZ dual therapy

Event	**Aml/Val HCTZ N = 136**	**Aml HCTZ N = 208**
AEs; n (%)	46 (33.8)	69 (33.2)
Edema peripheral	19 (14.0)	37 (17.8)
Nasopharyngitis	4 (2.9)	2 (1.0)
Headache	2 (1.5)	5 (2.4)
Dizziness	2 (1.5)	1 (0.5)
Syncope	2 (1.5)	0 (0.0)
Cough	1 (0.7)	4 (1.9)
Diarrhea	1 (0.7)	3 (1.4)
Viral infection	1 (0.7)	2 (1.0)
Paresthesia	0 (0.0)	2 (1.0)
Joint swelling	1 (0.7)	2 (1.0)
Dyspepsia	0 (0.0)	3 (1.4)
Flushing	0 (0.0)	3 (1.4)
Upper respiratory tract infection	0 (0.0)	2 (1.0)
Urinary tract infection	0 (0.0)	3 (1.4)
Hypokalemia	0 (0.0)	2 (1.0)
Arthralgia	0 (0.0)	2 (1.0)
Neck pain	0 (0.0)	2 (1.0)

Safety and tolerability

Both treatment arms were well tolerated. The overall incidence of AEs was similar between the triple and dual therapies (Table 3). Peripheral edema was the most frequently reported AE, which occurred at a slightly lower frequency in the presence of Val (Aml/Val+HCTZ: n = 19, 14.0%; Aml+HCTZ: n = 37, 17.8%).

Amongst patients who received HCTZ add-on at week 4, 1.7% (n = 6) of patients discontinued the study prematurely (Aml/Val+HCTZ; 1.5% [n = 2], Aml+HCTZ: 1.9% [n = 4]) due to AEs. There were no deaths during the entire course of the study. Serious AEs were also not reported in any treatment group from week 4 to week 8.

DISCUSSION:

Current hypertension treatment guidelines state that dual combination therapy be considered as initial therapy in patients with msBP ≥ 20/10 mmHg above goal.1,2 Furthermore, recent outcome trials suggest that the percentage of patients requiring three or more antihypertensive drugs to achieve BP control can range from 23%–52% depending on the trial.5,14–16

In this study, patients with stage 2 hypertension were randomized to initiate therapy with either dual Aml/Val therapy or Aml monotherapy with the addition of HCTZ to either regimen if BP remained uncontrolled. Triple therapy with Aml/Val+HCTZ 10/160/12.5 mg provided clinically and statistically significant additional BP reductions compared with the dual therapy with Aml+HCTZ 10/12.5 mg (*P* < 0.0001). Similarly, Aml/Val+HCTZ triple therapy produced greater BP reductions compared with Aml+HCTZ dual therapy in diverse patient

populations, including patients regardless of age, diabetic status, BMI, or race. These results are consistent with those reported by Calhoun et al wherein triple therapy with Aml/Val/HCTZ at a dose of 10/320/25 mg was shown to have superior efficacy compared with Aml/Val 10/320 mg, Val/HCTZ 320/25 mg, and Aml/HCTZ 10/25 mg dual therapies in a parallel-design trial, where patients were randomized to the four treatment groups.19 The patients on triple therapy achieved a mean SBP reduction of 40–50 mmHg, which was clinically and statistically greater than that with the dual component therapies.19 In the present study, a sequential antihypertensive treatment approach dependent on BP level achieved was followed, enabling the assessment of the efficacy and safety of adding a third agent in those patients initiated on dual therapy.

Hypertension is a multifactorial disease and the results of this study confirm that combining therapies with different mechanisms of action can additively reduce BP. Both Aml and Val are vasodilators that work through different mechanisms. Aml blocks calcium channels in vascular smooth muscle and Val blocks the binding of angiotensin II to the angiotensin type 1 receptor. The antihypertensive efficacy of calcium channel blockers (CCBs), however, is reduced by the associated activation of the renin–angiotensin system (RAS) and the sympathetic nervous system.20 Coadministration of an angiotensin receptor blocker (ARB) can effectively prevent such responses.

In this study, the response to HCTZ was dependent on the initial treatment, ie, Aml/Val vs Aml. The benefit of adding HCTZ was greater in patients treated with Val. This may be explained by the fact that diuretics decrease intravascular volume, activating RAS resulting in a diminished antihypertensive response. This counter-regulatory effect is prevented in the presence of an ARB. In previous studies, Val and HCTZ in combination have demonstrated additional BP lowering effects compared with each of the component monotherapies.21,22 While diminished efficacy of CCBs has been reported with concomitant diuretic therapy, other controlled studies have reported additional antihypertensive efficacy with a CCB and diuretic combination.23,24

Adding HCTZ to Aml/Val was not only effective in lowering BP, but was also well tolerated. Treatment discontinuations and the incidence of AEs were low with triple therapy and no difference was observed compared with dual therapy. The most frequently reported AE was peripheral edema, which appeared to be attenuated in the presence of Val.

Therapies combining drugs with complimentary mechanisms of action have also been recommended because they may attenuate certain AEs like the peripheral edema associated with CCBs and the hypokalemia associated with thiazide diuretics.25,26 For example, Val has previously been reported to reduce the incidence of hypokalemia associated with HCTZ and the peripheral edema associated with Aml.21,27 Moreover, it has been suggested that combining different drugs in a single pill may lead to better compliance and hence better BP control.28,29

CONCLUSION:

This study provides relevant information as it follows the clinical practice of prescribing a third antihypertensive agent in a step-wise manner to initial dual therapy depending on BP levels of the patient. The present analyses, however, have certain limitations: 1) this was a *post hoc* analysis of a study not designed to evaluate the efficacy of triple therapy vs dual therapy; 2) patients were not randomized to receive Aml/Val/HCTZ and Aml/HCTZ; and 3) the duration of the treatment with triple therapy was four weeks. In conclusion, triple combination therapy with Aml/Val/HCTZ provides significantly greater BP reductions and is well tolerated compared with Aml/HCTZ dual therapy in stage 2 hypertension and can provide additional benefits in patients who require more than two agents to reach their target BP.

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