Effets d'une association fixe Amlodipine/Valsartan sur la pression artérielle centrale et la rigidité artérielle chez les patients hypertendus

Effect of fixed association Amlodipine/Valsartan on Central blood pressure and arterial stiffness parameters in hypertensive patients

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Résumé

Notre objectif était d'analyser l'effet d'une association fixe (SPC) d'Amlodipine et de Valsartan sur la rigidité artérielle et les paramètres de réflexion de l'onde de pouls chez les patients hypertendus mal contrôlés par une monothérapie. Cette étude, prospective et observationnelle, a été menée dans le service de cardiologie de l'hôpital Charles Nicolle de Tunis, en Tunisie. Des hypertendus âgés de moins de 70 ans, sous une monothérapie pendant plus d'un mois sans atteindre l'objectif de pression artérielle (PA), ont été mis sous une SPC d'Amlodipine et Valsartan . Quatre visites ont été programmées. La PA périphérique (PAP) et la PA centrale (PAC) ont été mesurées à chaque visite. La vitesse de l'onde de pouls (cf-PWV) a été évaluée chez tous les patients au début de l'étude et réévaluée à 6 mois chez les diabétiques et/ou ayant une vitesse de l'onde de pouls initiale ≥ 12 m/s. Sur les 248 patients éligibles, 93 ont terminé l'étude. Après six mois, on a constaté une diminution significative de la PAP systolique avec -19,13 mm Hg ($p < .00001$), et de la PACsystolique avec -16,42 mm Hg ($p < .00001$). Chez les patients diabétiques et/ou ayant un PWV ≥ 12 m/s, Nous avons observé une diminution significative de la PAC systolique de -16,42 mm Hg ($p < .00001$), du cf-WPV de -1,38m/s ($p < .00001$) et de l'indice d'augmentation (Aix) de -2,42% ($p < .00001$). En conclusion, une SPC d'amlodipine et valsartan était efficace pour assurer un contrôle de la PA centrale et périphérique.

Mots-clés

hypertension; rigidité artérielle; pression artérielle centrale

Summary

We aimed to analyze the effect of single pill combination (SPC) of Amlodipine and Valsartan on arterial stiffness and wave reflection parameters in hypertensive patients who fail to control blood pressure with mono-therapy. This study, a prospective and observational, was conducted in the Cardiology Department of Charles Nicolle University Hospital of Tunis, Tunisia. Hypertensive patients under 70- year-old, receiving low dose mono-therapy longer than 1 month without achieving goal blood pressure, were started on a single pill combination (SPC) of Amlodipine and Valsartan. Four visits were programmed. Enrolled patients had peripheral (PBP) and central blood pressure (CBP) measurements at each visit. Pulse wave velocity (cf-PWV) was evaluated in all patients at baseline and was re-evaluated at 6 months in patients with diabetes and/or PWV ≥ 12 m/s. Of 248 eligible patients only 93 finished the study. After six months, there was a significant decrease in PSBP with -19,13 mm Hg ($p < .00001$), and in CSBP with -16,42 mm Hg ($p < .00001$). In patients with diabetes and/or PWV ≥ 12 m/s, initially, there was an improvement in arterial stiffness with a significant decrease in CSBP with -16,42 mm Hg ($p < .00001$), in cf-WPV with -1,38m/s ($p < .00001$) and in Augmentation index (Aix) with -2,42% ($p < .00001$). In conclusion, therapy based on SPC of Valsartan/amlodipine was effective in providing extensive BP control (office, and central BP).

Keywords

hypertension; arterial stiffness; central blood pressure

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INTRODUCTION

In recent decades, prospective cohort studies suggest that arterial stiffness and wave reflection parameters are strong and independent predictors of cardiovascular and all-cause mortality in healthy and hypertensive patients. (1,2)

Arterial stiffness is associated with the incidence of hypertension and assessed by measuring pulse wave velocity (PWV), based on the theory that stiffer conduit (3) arteries propagate the pulse waves faster. Arterial stiffness is an independent risk of vascular outcomes as well. (4,5)

Among recommended therapies in many hypertension guidelines, Calcium Channel Blockers (CCBs) and Angiotensin Receptor Blockers (ARBs) are both first-line antihypertensive medicines. Versus other CCBs, Amlodipine, one of the long-acting dihydropyridine calcium antagonists, has a higher vascular selectivity and lesser negative inotropic effect. Valsartan is a kind of nonpeptide angiotensin II antagonist that also has long-term action.

According to former guidelines, a low dose of either CCBs or ARBs is a recommended therapy for mild to moderate hypertension. (6) However, when it fails to achieve the goal of blood pressure, the following optimal treatment strategy remains disputed. One option is the use of a single pill combination (SPC) of the two drugs.

This study aimed to access the effect of SPC of Amlodipine and Valsartan on peripheral and central blood pressure, arterial stiffness, and wave reflection parameters in hypertensive patients who fail to control blood pressure with mono-therapy.

METHODS

This study, prospective and observational, was conducted in the Cardiology Department of Charles Nicolle University Hospital of Tunis, Tunisia. The approval from the Ethics Committee of Charles Nicolle University Hospital was obtained to conduct the study. Inclusion criteria were: hypertensive patients, below 70- year-old, receiving low dose mono-therapy longer than one month without achieving goal blood pressure (BP< 140/90 mm Hg). Participants with secondary hypertension, severe hypertension (either SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg), evidence of a cerebrovascular accident, myocardial infarction, heart failure, aneurysm, arterial dissection, and malignant arrhythmia in 6 months were excluded from this study. Patients were also excluded if they had known hypersensitivity or contraindications to valsartan or amlodipine, atrial fibrillation, and chronic renal disease.

Eligible patients were started on a SPC of Amlodipine and Valsartan. Four visits were programmed: enrollment visit (T0), after one month (T1), after three months (T2), and after six months (T3). Enrolled patients had peripheral and central blood pressure measurements at T0, T1, T2, and T3 visits. Pulse wave velocity (cf-PWV) was evaluated in all patients at baseline and re-evaluated at six months (T3) in patients with high diabetes and/or PWV12 m/s.

The enrollment period was from September 2019 to August 2020. Informed consent was obtained from all of the patients before entering the study.

Data collection

Questionnaires, physical examinations, and blood samples were performed and collected after participants signed informed consent. Specially trained doctors collected data. BMI was calculated using the following formula: weight / height2 (kg/m^2).

Critères d' exclusion

Les patients hyperthyroïdiens qui présentaient une insuffisance coronaire en rapport avec autre pathologie que l'hyperthyroïdie étaient non inclus

Central Blood pressure and pulse wave velocity measurement:

In a first step, we determined the central hemodynamic parameters. To perform the measurement, a standard brachial cuff is used to measure brachial systolic and diastolic pressures (three measurements) allowing the capture of a brachial pulse wave after having obtained a good pressure signal over several cardiac cycles. The peripheral pulse wave is then analyzed by SphygmoCor®XCEL using a calibrated transfer function to provide the central pulse wave.

Subsequently, the following central hemodynamic parameters were calculated:

Central Systolic Blood Pressure (CSBP).

Central diastolic blood pressure (CDBP).

Central Pulsed Pressure (CPP).

The augmented pressure (AP), which is calculated as follows: AP (ΔP) = the late systolic peak (P2) - the early systolic peak (P1), both peaks are identified on the pressure curve (Figure 1).

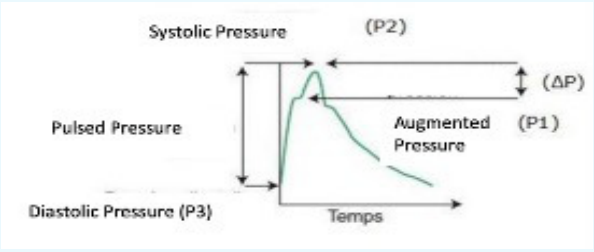

Figure 1. Pulse wave analysis

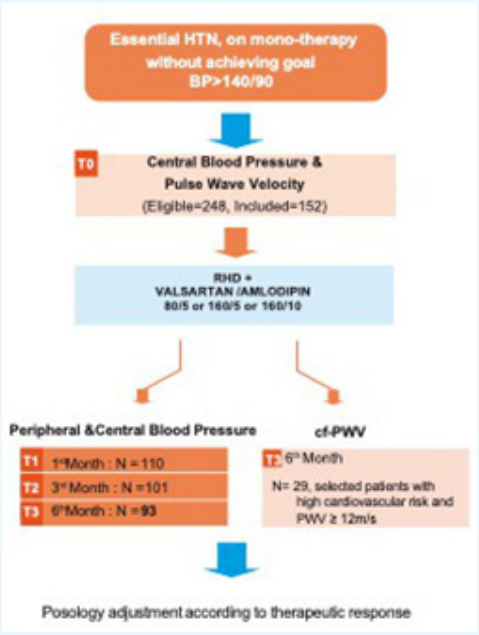

Figure 2. Study schema

Physiologically, the arterial pulse wave is composed of two waves, one incident and one reflected.

By convention, the AP is negative if the encounter between the reflected and incident wave occurs after the systolic peak (the largest), and it is positive if the encounter between these two waves occurs before the systolic peak.

The index of increase (Aix): this is the quotient of AP by PPc (Aix = AP/PPc).

In a second step, we measured the cf-WPV. The cf-WPV measurement is based on the «foot-to-foot» method, which consists of calculating the time (Δt) between the feet of the pressure waves recorded at the carotid and femoral artery. Then the distance (d) between the two measurement sites is measured. Thus, the cf-WPV is calculated: WPV= d/Δt.

All patients were requested to abstain from caffeine-containing food for at least 30 minutes and rest in a quiet room for at least 5 minutes before the measurement. The subjects were examined in a supine position with monitoring cuffs wrapped around both upper arm and leg, which allowed simultaneous recording.

Statistics

Continuous variables are expressed as mean ± SD or medians with interquartile range according to the distribution. Categorical variables are presented as frequencies and percentages. Mean values were compared by the Z test. SPSS version 16 (SPSS Inc., Chicago, IL, U.S.) was used for all statistical analyses and $p < 0.05$ was considered significant.

RESULTS

A total of 248 patients were eligible, 152 patients accepted to enter the trial. Of the 152 subjects studied at baseline, 59 did not reach the end of the study. We analyzed data of the remaining 93 patients. Twenty-nine patients had high cardiovascular risk and cf-PWV 12 m/s.

The clinical characteristics of patients are presented in Table 1.

Tableau 1. Population Baseline characteristics

Age, years	54,38
Male, No. (%)	55 (59,1)
BMI, Kg/m2	26,2
Smoking, No. (%)	28 (30,1)
Diabetes, No. (%)	13 (13,9)
Coronary artery disease, No. (%)	16 (17,2)
Dyslipidemia, No. (%)	26 (27,9)
Hypertension Grade 1, No. (%)	52 (55,9)
Serum creatinine, µmol/l	82,98
Heart rhythm (bpm)	76
PSBP (mmHg)	158,18
PDBP (mmHg)	92,38
PPP (mmHg)	65,8
CSBP (mmHg)	140,66
CDBP (mmHg)	91,50
CPP (mmHg)	48,83
AP (mmHg)	12,73

(PSBP: peripheral systolic blood pressure; PDBP: peripheral diastolic blood pressure; PPP: peripheral pulsed pressure, CSBP: central systolic blood pressure; CDBP: central diastolic blood pressure; CPP: central pulsed pressure; AP: Augmented Pressure)

Peripheral SBP, DBP, and PP are presented in Figure 3, at baseline (T0), at 1 month (T1), 3 months (T2) and 6months (T3). Between T0 and T3 there was a significant decrease in PSBP with -19,13 mm Hg ($p < .00001$), PDBP with -12,05 mmHg ($p < .00001$) and PPP with -9,08 mmHg ($p < .00001$).

Figure 3. Total population (N=93) Peripheral blood pressure parameters evolution (mmHg) (PSBP: peripheral systolic blood pressure; PDBP: peripheral diastolic blood pressure; PPP: peripheral pulsed pressure)

Central SBP, DBP, PP, AP and Aix are presented in Figure 4, at baseline (T0), at 1 month (T1), 3 months (T2) and 6months (T3). Between T0 and T3 there was a significant decrease in CSBP with -16,42 mm Hg ($p < .00001$), CDBP with -11,96mmHg ($p < .00001$), CPP with -7,44 mmHg ($p < .00001$) and AP with -2,8 mmHg ($p < .00001$). There was also a significant decrease in augmentation index (Aix) with -2,6% ($p < .00001$).

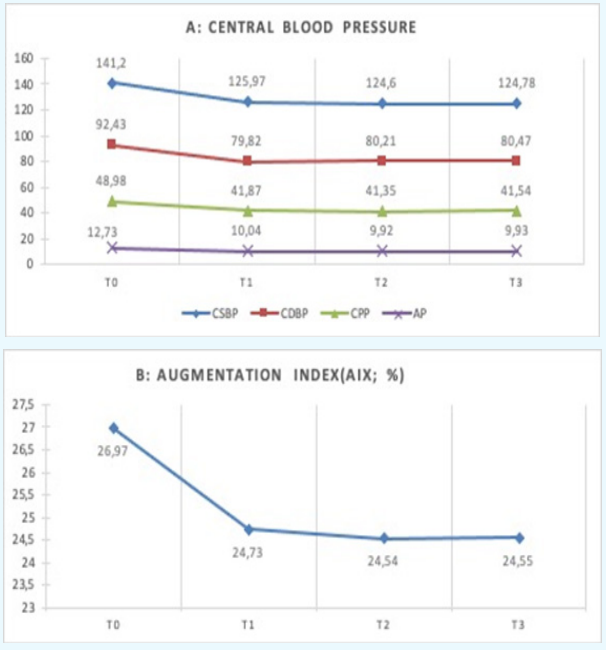

Figure 4. Total population (N=93) Central blood pressure parameters evolution: A: central blood pressure (mmHg); B: Augmentation index (CSBP: central systolic blood pressure; CDBP: central diastolic blood pressure; CPP: central pulsed pressure; AP: Augmented Pressure)

In patients with initial cf-PWV 12 m/s, (29 patients), Central SBP, DBP and cf-WPV are presented in Figure 5 and Figure 6 at baseline (T0), and 6months (T3). There was an improvement in arterial stiffness with a significant decrease in CSBP with -16,42 mm Hg ($p < .00001$), in CDBP with -11,96mmHg ($p < .00001$), in cf-WPV with -1,38m/s ($p < .00001$) and in Aix with -2,42% ($p < .00001$).

Only five patients (5,3%) reported side effects of this association: 4 patients had inferior limb edema and one patient reported digestif discomfort.

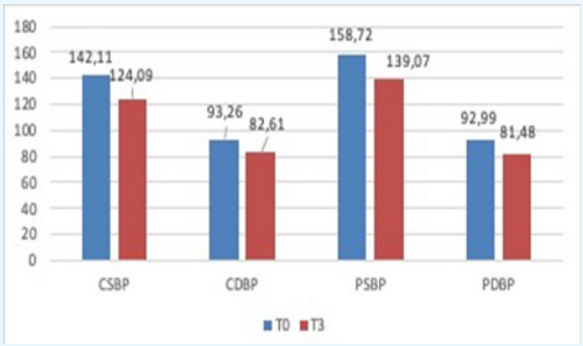

Figure 5. Central and peripheral blood pressure (mmHg) evolution (CSBP: central systolic blood pressure; CDBP: central diastolic blood pressure; PSBP: peripheral systolic blood pressure; PDBP: peripheral diastolic blood pressure)

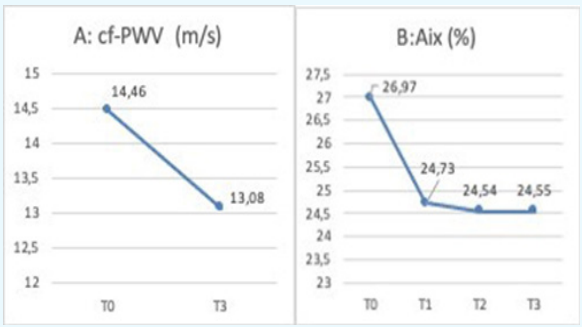

Figure 6. Arterial stiffness parameters evolution.
(A: cf-PWV: carotid-femoral pulse wave velocity; B: Aix: augmentation index)

DISCUSSION

In our study, all patients significantly lowered their office blood pressure (PSBP, PDBP, and PPP) since the first month after 4-week treatment with SPC of Amlodipine and Valsartan. This reduction persisting until the sixth month of the treatment was associated with a significant decrease in central blood pressure parameters. Besides,

patients with high cardiovascular risk and cf-PWV with a SPC of Amlodipine and Valsartan achieved an improvement in arterial stiffness with a mean reduction in cf-PWV of 1,38m/s in six months.

Invasive central blood pressure is the «gold standard» for determining blood pressure-related organ damage and cardiovascular consequences. (7) However, due to its measurement difficulty and discontinuity, it is being replaced by clinical blood pressure, a convenient and non-invasive measurement used in daily practice. Numerous large clinical studies have demonstrated that patients may benefit from achieving the clinical target blood pressure that has been adopted and codified in hypertension guidelines. (8) However, several studies have shown that lowering BP alone is not responsible for all the harms and consequences of hypertension in practice, suggesting that other mechanisms or residual risks may exist after BP increases. (9) Therefore, other potential indicators must be considered when selecting a therapy and evaluating its effect.

Central blood pressure and central PP were reduced, which may be associated with better CV outcomes as previously suggested by some investigators. (8)

Dihydropyridine calcium channel blockers and angiotensin II receptor blockers are expected to reduce central and peripheral blood pressure (9-15), and our results support this finding.

The reduction in central blood pressure over peripheral blood pressure may be due to improvements in arterial stiffness, changes in the amplitude/time of wave reflections, or both. Observing that AP is a direct marker of altered wave reflection in the absence of Aix modification, active drugs reduce the significance of wave reflection changes.

Long-term beneficial effects of lowering arterial blood pressure on cardiovascular events are well documented in large clinical trials in hypertensive patients (16-22). Optimal blood pressure should be the goal when initiating antihypertensive or antihypertensive drug therapy. However, it must be remembered that, at least in theory, aggressively lowering blood pressure can impair blood flow to central and peripheral organs, especially in cases of severe coronary artery disease. (23-25) In general, however, lower blood pressure is associated with better outcomes. Different vasodilators act differently on arteries and arterioles. (26)

Arteriolar vasodilators primarily increase arteriolar caliber, thus reducing peripheral resistance and mean arterial pressure through their action on arteriolar smooth muscle cells. Arterial vasodilators primarily relax smooth muscle cells in muscular arteries, thus reducing PWV, wave reflection amplitude and duration, and lowering central systolic and pulse pressure more than the arm cuff pressure component. (16, 17, 24, 26, 27)

Currently available vasodilators have little direct effect on elastic arteries, and although drugs that directly reduce elastic arterial stiffness are being developed, none are currently available for routine clinical use. A sharp reduction in the augmentation index can be achieved by drugs that actively dilate the muscular arteries, accompanied by a passive action on the elastic arteries. (24) These individual actions reduce the propagation of pressure waves (incident and reflection) along the entire arterial tree and improve wave reflection properties. Vasodilator drugs such as ACEIs, ARBs, calcium channel blockers, nitrates, phosphodiesterase type 5 inhibitors, nitric oxide, and omatrilat reduce arterial stiffness and PWV, thereby returning from the periphery by delaying reflected waves The heart reduces wave reflections while reducing its amplitude and contraction duration. (16, 27)

The effects of vasodilators on brachial and radial systolic and pulse pressures are much less pronounced than their effects on central blood pressure. (24)

In the Regression of Arterial Stiffness in a Controlled Double-Blind Study (REASON) trial, (16,17) the ACEI perindopril decreased synthesized aortic systolic and pulse pressures significantly more than the beta-blocker atenolol even though the drugs lowered elastic artery PWV by the same amount.

Based on the above observations, the apparent 'stress-independent' benefit of vasodilators in clinical trials such as the Heart Outcome Prevention Evaluation (HOPE) trial (28) may be largely attributable to unmeasured but significantly reduced central (but not Peripheral) systolic and pulse pressure. Thus, beneficial effects of ACEIs, including regression of LV hypertrophy, (29) are not independent of changes in arterial BP simply, that the sphygmomanometer method does not measure the

"right" BP (that is, the pressure the heart pumps against).

The same reasoning could easily explain why the ARB losartan was more effective than atenolol in reducing LV mass and cardiovascular mortality in the LIFE study (Losartan Intervention For Endpoint Reduction in Hypertension). (21, 22) In LIFE study, atenolol and losartan reduced brachial systolic and pulse pressure by equal amounts. However, in this study, atenolol decreased aortic systolic and pulse pressure by 28 and 11 mmHg, respectively, while losartan decreased aortic systolic and pulse pressure by 40 and 23 mmHg, respectively. Atenolol had little effect on radial and aortic augmentation indices, whereas losartan had a significant lowering effect. Some limitations of this study should be recognized.

First, the sample size of this study was relatively small.

Second, the study was fairly short, so cardiovascular events and other parameters of renal and vascular function were not included. Therefore, more patients should be recruited and comprehensive indicators should be applied in future studies to assess this treatment effect. Finally, whether other CCBs, ARBs, or even other types of antihypertensive drugs have similar effects requires further comparative studies.

To our knowledge, this is the first study in Tunisia that is interested in central arterial pressure and arterial stiffness, which are the most predictive indicators of overall cardiovascular risk, and uses a new technology for the first time in Tunisia: the «noninvasive Measurement of central arterial pressure, arterial pressure and arterial stiffness».

CONCLUSION

In conclusion, valsartan/amlodipine SPC is effective in providing office and central BP control and in reducing arterial stiffness. Effective blood pressure control therapy resulted in significant resolution of target organ damage.

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