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Possible beneficial effects of amlodipine, lisinopril, and their Combination on lipid profile in hypertensive patients

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Summary

It is well known that monotherapy does not provide therapeutic response in all hypertensive. Some patients show an excellent response, while in others there is a poor response. Combination antihypertensive therapy is administered when blood pressure is inadequately controlled by monotherapy to achieve a balanced and additive antihypertensive effect with minimum adverse effects. Both angiotensin converting enzyme (ACE) inhibitors and dihydropyridine type of calcium antagonists are well established and widely used in monotherapy. An understanding of differences in the mechanism of action of these agents allows a logical approach for the use of these agents as a combination therapy. This study was designed to evaluate the possible beneficial effects of long acting calcium channel blocker, amlodipine and the long acting Angiotensin converting enzyme (ACE) inhibitor, lisinopril given either alone or in combination in patients with essential hypertension on lipid profile (LDL-C and HDL-C) and on other parameters using a randomized double blind, crossover study. The study includes 150 patients with systolic blood pressure (SBP)>140 mmHg and diastolic blood pressure (DBP) >90 mmHg received amlodipine 5 mg, lisinopril 5 mg and their combination prior randomization schedule. Systolic, diastolic blood pressure and pulse rate were recorded at weekly intervals while, serum levels of urea, creatinine, LDL-C and HDL-C where recorded at monthly intervals, the duration of this study was 3 months. Results were obtained using paired students t-test, differences were considered significant with ($p<0.05$).

A significant decline in SBP and DBP in all treatment groups ($p<0.05$) was recorded, the reduction tend to be more pronounced in the combination group. Moreover, there was a significant effect of combination on the heart rate, serum level of urea and creatinine, beside that, the level of HDL was significantly elevated with amlodipine and combination. We concluded that combination had additional blood pressure lowering effect when compared either with amlodipine or lisinopril alone, in addition to the greater effect on lipid profile which demonstrated that this combination is potential antiatherosclerotic agent.

التأثير المحتمل المفيد للأملودبين لزنوبرل ومزيجهما على شكل الدهون, أضافة الى تقييمهم لدى المرضى المصابين بأرتفاع ضغط الدم.

فاديه يعقوب الحمداني

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الخلاصة

من المعروف جيدا" إن العلاج المنفرد لايزود الاستجابة العلاجية لدى كل من لديهم ارتفاع ضغط الدم. بعض المرضى يعطون استجابة ممتازة, بينما آخرين تكون استجابتهم ضعيفة.العلاج المركب ضد ارتفاع ضغط الدم يعطى عندما لاتكون هناك سيطرة كافية على ضغط الدم بالعلاج المنفرد لنحصل على تأثير متوازن وإضافي ضد ارتفاع ضغط الدم مع حد أدنى من التأثيرات الجانبية.

كلا المانعون للأنزيم المحول للأنجيوتنسين و نوع الدايهايدروبايردين من المقاومات للكالسيوم قد أسست جيدا" واستعملت بشكل واسع في العلاج المنفرد. أن فهم الاختلافات في آلية العمل لهذه العوامل يسمح بنظرة منطقية في استعمال هذه العوامل كعلاج مركب.

هذه الدراسة صممت لتقييم التأثير المحتمل المفيد لحواجز قنوات الكالسيوم الطويلة الأمد, املودبين و المانع للأنزيم المحول للأنجيوتنسين الطويل الأمد, لزنوبرل أعطيت أما لوحدهما أو في مركب لدى مرضى مع ارتفاع ضغط الدم الأساسي على شكل الدهون (البروتين الدهني واطئ الكثافة والبروتين الدهني عالي الكثافة) وعوامل أخرى مستعملين دراسة متعاقبة, مستترة, مضاعفة

وعشوائية.الدراسة تضم 150 مريض مع ضغط دم انقباضي > 140ملم زئبقي وضغط دم انبساطي > 90ملم زئبقي استلموا املودبين 5 ملغم, لزنوبرل 5 ملغم ومركبهما قبيل البرنامج العشوائي.

ضغط الدم الانقباضي والانبساطي مع معدل النبض سجلت كل اسبوع, بينما مستوى اليوريا , الكرياتنين, البروتين الدهني واطئ الكثافة والبروتين الدهني عالي الكثافة فقد سجلت كل شهر, مدة الدراسة كانت 3 أشهر. النتائج تم تحصيلها مستعملين بيرد ستيودينت ت تيست, الاختلافات اعتبرت مؤثرة مع (احتمالية < 5..,.).انخفاض مؤثر في ضغط الدم الانقباضي والانبساطي في كل مجاميع العلاج(الاحتمالية < 5..,.) قد سجل, الانخفاض بدا أكثر وضوح في مجموع المركب. علاوة على ذلك, كان هناك تأثير مؤثر للمركب على نبضات القلب,مستوى اليوريا و مستوى الكرياتنين, إلى جانب ذلك, مستوى البروتين الدهني عالي الكثافة أرتفع بشكل مؤثر مع الاملودبين والمركب.

استنتجنا أن المركب له تأثير خافض أضافي على ضغط الدم عندما يقارن أما مع الأملودبين أو لزنوبرل لوحدهما, إضافة إلى تأثير أكبر على شكل الدهون والذي يظهر أن المركب عامل محتمل ضد تصلب الشرايين.

Introduction

ACE inhibitors and a dihydropyridine type of calcium antagonists are well established and widely used as monotherapy in patients with essential hypertension.[1] Earlier studies combining short acting drugs from these classes require multiple dosing and were associated with poor compliance. Availability of longer acting compounds allows once daily administration to avoid the inconvenience of a multiple daily dose.[1,2]

Calcium antagonists have vasodilatation effect and tend to increase plasma renin, therefore combination with an ACE inhibitor is theoretically sound.[3] Furthermore, they have been shown to have a diuretic and natriuretic effect, which again should combine well with ACE inhibitors.[4] Calcium antagonists and ACE inhibitors in combination reduce blood pressure more than either drug given alone; where the combination of nifedipine and captopril was found to be significantly more effective than the individual agents.[5] However the effect was short lived due to the short duration of action of both drugs. Moreover, combination therapy of 5 mg enalapril and 5 mg felodipine produced a significant decrease in both supine and erect blood pressure.[6] Longer acting compounds of both classes, like amlodipine and lisinopril, have now become available allowing once daily administration.

Hypertension is one of the major cardiovascular risk factors, independently of age, sex, or race. Arterial blood pressures, both systolic and diastolic, are correlated with the incidence of coronary heart disease and stroke. As the risk increases continuously within the pressure ranges, the risk in individuals with borderline hypertension is somewhat higher than that of normotensive individuals. [7] Little is known about the role of hypertension in the atherothrombotic process. It has been postulated that the excessively high pressure would damage the endothelium and increase its permeability. [8] In addition, hypertension could stimulate the proliferation of smooth muscle cells or induce the rupture of the plaque. The presence of a lesion in the target organs (left ventricular hypertrophy and/or microalbuminuria) is accompanied by an increase in cardiovascular risk. A number of clinical trials have demonstrated that a decrease in arterial blood pressure is associated with significant reductions in the rate of stroke and, to a lesser extent, in that of coronary events, circumstances that produce an overall decrease in cardiovascular mortality.[9] The association between serum cholesterol levels and the incidence of IHD has been demonstrated in experimental and epidemiological studies.[10,11] The relationship between cholesterol and IHD is continuous, gradual and highly intense.[10] The predictive value of the cholesterol level decreases with age, and actually is low from the sixth decade of life on. The risk attributed to hypercholesterolemia is due to low density lipoprotein cholesterol (LDL-C).

A number of intervention studies have demonstrated that the lowering of LDL-C by means of hypolipidemic agents is accompanied by significant reductions in cardiovascular morbidity and mortality, both in primary and secondary care. [12] An independent, inverse correlation between high density lipoprotein cholesterol (HDL-C) and the risk of IHD has been observed in several epidemiological studies.[13] The protection provided by HDL-C is independent of the LDL-C concentration. The National Cholesterol Education Program (NCEP) considers a HDL-C level below 40 mg/dL to be a risk factor, whereas concentrations over 60 mg/dL are reported to be a negative risk factor. [14]

The aim of the present study was to evaluate the possible beneficial effects of amlodipine and lisinopril, individually and in combination on lipid profile, and also to assess the effect of the above drugs on SBP and DBP in a double blind, randomized, crossover design, in patients with essential hypertension.

Materials and methods

Hundred and fifty out patients with essential hypertension attending Al-kadhimiyah Teaching Hospital; ward of internal medicine, were selected to participate in this study. The criteria for eligibility included patients their mean age was 63.1 years; 53% were female, there systolic blood pressure was >140 mmHg and a diastolic blood pressure was >90 mmHg. Patients with renal and hepatic impairment, pregnant women, or those who were taking oral contraceptives were excluded from the study. All patients gave their written informed consent for their participation in this institutional ethics committee approved study. Before inclusion into the study protocol, regular measurement of blood pressure was carried out at weekly intervals for four weeks. All information about each patient was recorded in the case sheet as shown in figure (I). All patients were studied on their usual diet and no dietary advice was given.

After blood pressure measurement, patients were divided into the following groups according to specific treatment regimen as follows:

- Group I- 50 patients with essential hypertension, their systolic blood pressure mean was 176.2 and diastolic blood pressure mean was 90.4. They were received 5 mg amlodipine tablet once daily and lasted for three months.
- Group II- 50 patients with essential hypertension their systolic blood pressure mean was 153.92 and diastolic blood pressure mean was 87.2. They were received 5 mg lisinopril once daily and lasted for 3 months.
- Group III- 50 patients with essential hypertension their systolic blood pressure mean was 174.3 and diastolic blood pressure mean was 92.32. They were received a combination of 5 mg amlodipine tablet and 5 mg lisinopril tablet and lasted for 3 months.

Each patient had blood taken in the first visit of starting each treatment regimen.

Blood pressure, pulse rate, respiratory rate, temperature were measured by EAGLE 1000 patient monitor and Chison 600 J. These parameters were determined according to the reading obtained from the patient monitor as shown in figure (II).

Serum levels of urea, creatinine, LDL-C, HDL-C, were measured using kits, for HDL-C, the supplied company was (Biolabo SA-France), for serum urea (Biomerieux-France) and for serum creatinine (Linear Chemicals-Spane).

Patients were asked if there had been any change in their presenting symptoms or development of new symptoms at each follow up visit. Patients were instructed to return unused medications at each follow up visit to know the compliance.

To test the differences between groups, paired Student's t-test were made. Differences were considered significant with $P<0.05$.

Name: Age: Sex: Job: Wt.:
Chief Complain and Duration:
History of Present illness:
Past Medical History: HT ☐ DM ☐ I.H.D ☐ Renal Failure ☐

T.B ☐ Asthma ☐

Family History ☐ DM ☐ I.H.D ☐ HPL ☐

Social History: Smoker ☐ Alcohol ☐ Fatty Diet ☐

Old Medication for Hypertension
New Medication for Hypertension

Follow up:

Date	B.P	PR	RR	Temp	ECG	Spo_2	Notes

Lab. Results:

Date	Urea	Creatinine	HDL	LDL	Protein in urine	Other lab. According condition	Notes

Figure (I): Case sheet of full information obtained from each patient

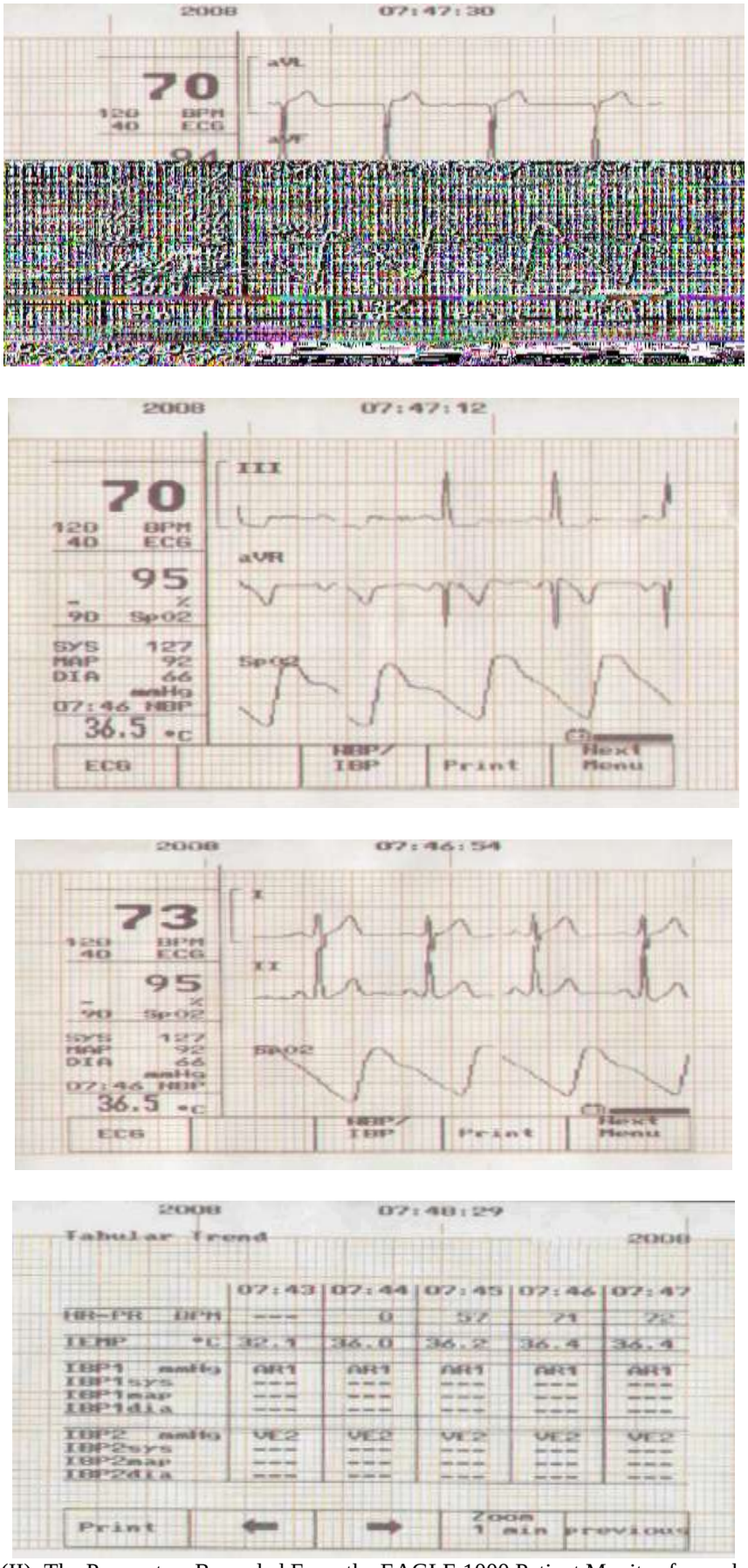


Figure (II): The Parameters Recorded From the EAGLE 1000 Patient Monitor for each patient

Results

A description of patients according to some clinical and laboratory parameters is given in tables (1, 2 and 3) Treatment with amlodipine provided a significant reduction ($p<0.05$) of both systolic, diastolic blood pressures, and significant reduction of pulse rate compared to their levels before starting the treatment. Moreover, treatment with 5 mg amlodipine tablet showed significant increase ($P<0.05$) in serum level of HDL-C; while there were no significant differences concerning serum levels of creatinine, urea and LDL-C ($P>0.05$) compared to their levels before starting the treatment, as shown in Table (1).

Treatment with lisinopril 5 mg also provided a significant reduction of both systolic and diastolic blood pressure compared to their levels before starting the treatment. ($p<0.05$); while there where no significant differences observed concerning pulse rate, serum levels of urea, creatinine, HDL and LDL ($p>0.05$) as shown in Table (2).

Treatment with combination provided more significant reduction of both systolic and diastolic blood pressure, and more significant reduction of pulse rate compared to their levels before starting the treatment.($p<0.05$). Moreover, combination therapy showed a significant increase in serum levels of urea and creatinine and much greater increase in serum level of HDL-C. ($p<0.05$), without any changes seen in the level of LDL-C ($p>0.05$) as shown in Table (3).

Table (1): Paired Samples Test of Amlodipine before and after treatment.

	Paired Differences					t	df	Sig.
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Systolic pressure before – Systolic pressure After	42.19121	12.29215	1.73837	38.69783	45.68460	24.271	49	.000*
Diastolis pressure before – diastolis pressure after	15.38488	12.10551	1.71198	11.94453	18.82523	8.987	49	.000
PR – PR A	2.92952	6.43845	.91053	1.09974	4.75931	3.217	49	.002
RR – RR A	.16200	1.24465	.17602	-.19173	.51573	.920	49	.362
Temp - TempA	.04447	.18282	.02586	-.00749	.09642	1.720	49	.092
Urea – Urea A	-2.58000	8.18246	1.15717	-4.90543	-.25457	-2.230	49	.030
Creat. – Creat.A	-.05330	.17471	.02471	-.10295	-.00365	-2.157	49	.036
HDL – HDL A	-3.13000	6.72174	.95060	-5.04030	-1.21970	-3.293	49	.002
LDL – LDL A	-4.43000	20.73571	2.93247	-10.32302	1.46302	-1.511	49	.137

*P<=0.05 Significant, P<0.05 highly significant, P>0.05 non-significant

Figure (1): mean differences of amlodipine for each parameter.

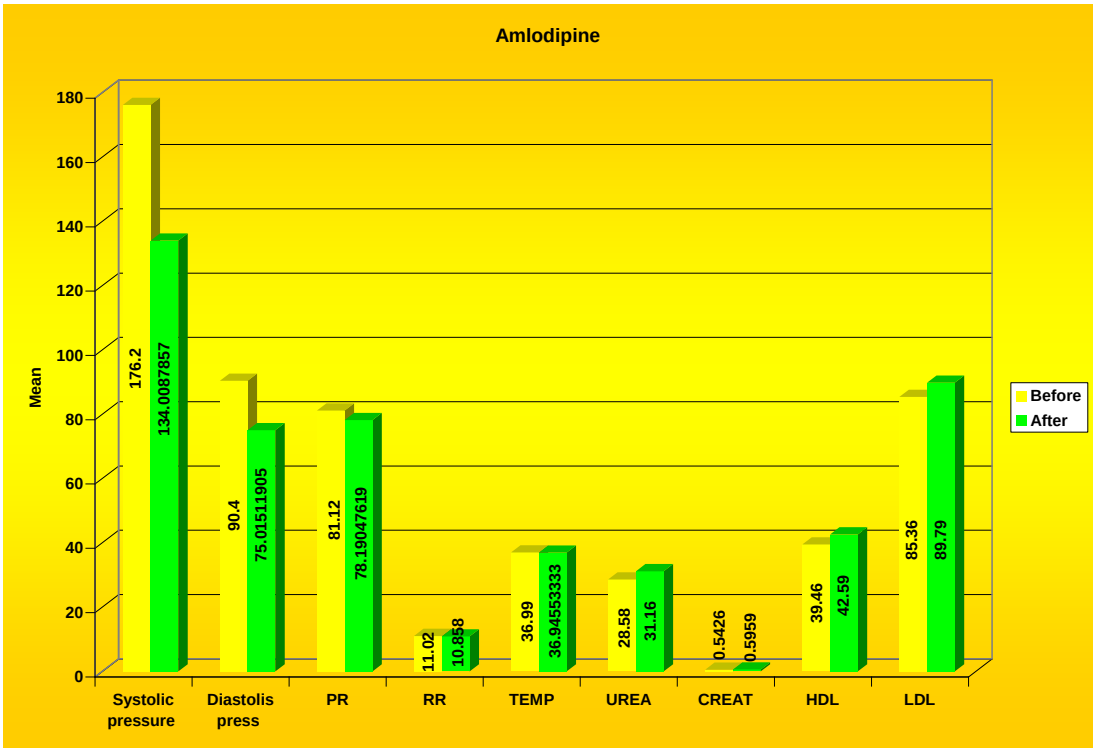


Table (2) Paired Samples Test of Lisinopril before and after treatment.

	Paired Differences					t	df	Sig.
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Systolic pressure before – Systolic pressure after	27.88767	18.07751	2.55655	22.75010	33.02524	10.908	49	.000
Diastolis pressure before – diastolis pressure after	11.06729	10.79429	1.52654	7.99958	14.13499	7.250	49	.000
PR – PR A	1.26952	12.92725	1.82819	-2.40436	4.94341	.694	49	.491
RR – RR A	-.14805	1.18149	.16709	-.48382	.18773	-.886	49	.380
Temp - Temp A	.04656	.33227	.04699	-.04787	.14099	.991	49	.327
Urea - Urea A	1.08031	12.03788	1.70241	-2.34081	4.50144	.635	49	.529
Creat – Creat A	-1.09102	7.52312	1.06393	-3.22907	1.04703	-1.025	49	.310
HDL - HDL A	4.04386	16.10852	2.27809	-.53413	8.62185	1.775	49	.082
LDL – LDL A	-.48343	10.62411	1.50248	-3.50277	2.53591	-.322	49	.749

Figure (2) :mean differences of Lisinopril for each parameter.

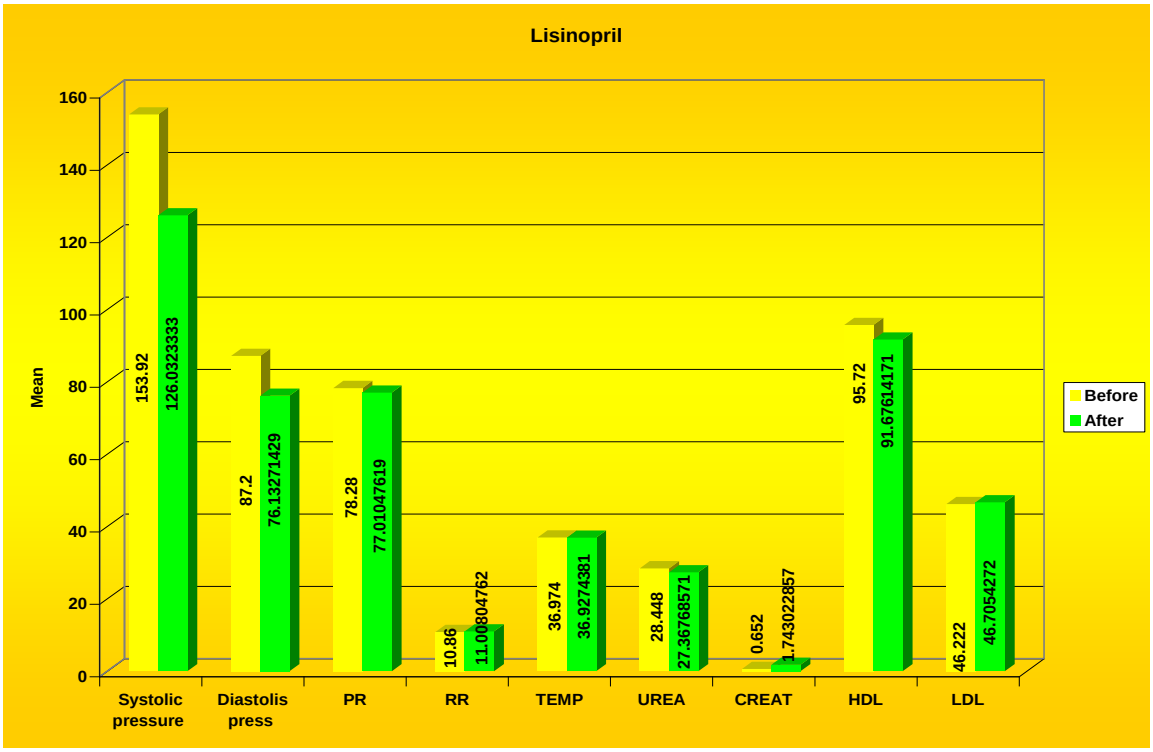
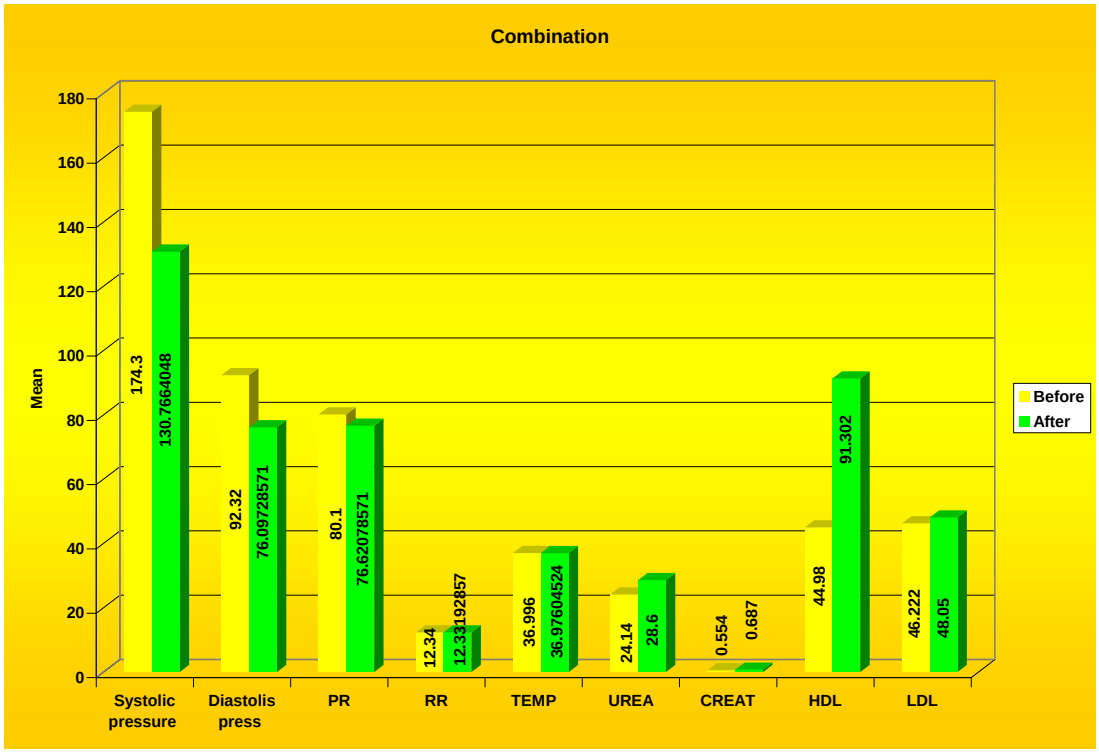


Table (3) Paired Samples Test combination Paired Samples Test before and after treatment.

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	SBP –SBP A	43.53360	18.18002	2.57104	38.36689	48.70030	16.932	49	.000
Pair 2	DBP – DBP A	16.22271	13.07136	1.84857	12.50787	19.93755	8.776	49	.000
Pair 3	PR – PR A	3.47921	7.61410	1.07680	1.31531	5.64312	3.231	49	.002
Pair 4	RR – RR A	.00807	2.29602	.32471	-.64445	.66059	.025	49	.980
Pair 5	Temp- Temp A	.01995	.21397	.03026	-.04086	.08077	.659	49	.513
Pair 6	Urea – Urea A	-4.46000	8.59214	1.21511	-6.90186	-2.01814	-3.670	49	.001
Pair 7	Creat. – Creat. A	-.13300	.20717	.02930	-.19188	-.07412	-4.540	49	.000
Pair 8	HDL – HDL A	8.99800	15.86191	2.24321	4.49009	13.50591	4.011	49	.000
Pair 9	LDL – LDL A	-3.07000	12.07291	1.70737	-6.50108	.36108	-1.798	49	.078

Figure (3): Mean differences of Combination for each parameter.



Discussion

Many antihypertensive agents are available in the market. Any of these drugs when used alone as a monotherapy are effective in only 40%–60% of patients with hypertension.[15] Several studies reported that, combination of two different classes of antihypertensive agents are useful and promising in controlling blood pressure in patients with hypertension.[16,17]. Calcium channel blockers and ACE inhibitors in combination reduce blood pressure more than either drug alone. [5] In the present study, we observed more effective lowering of blood pressure with amlodipine and lisinopril in combination. Singer *et al* demonstrated a greater blood pressure lowering effect when nifedipine and captopril were combined. [5] However; they found the effect of the combination to be short lasting. Similar observations were also made in a small group of patients who were on a captopril and nifedipine combination.[18,19] In the present study, the combination of long acting drugs of the two classes, namely amlodipine and lisinopril, reduced blood pressure more than either drug alone even 24 hours after dosing. This clearly shows that the combination has a marked additional and long lasting effect on blood pressure. Perhaps the most efficient and conceptually attractive approach in the treatment of patients in whom ACE inhibitor or calcium channel blocker monotherapy fails, is to combine the two agents, thereby blocking the major vasoconstrictive mechanisms.[20] The efficacy of a calcium channel antagonist is enhanced by concomitant use of either ACE inhibitor, or methyldopa, or α-adrenergic receptor blockers.[21] Ninety percent of patients with essential hypertension are controlled by combination of an ACE inhibitor with either a calcium channel blocker, α-adrenergic receptor blocker, or diuretic.[22] Isolated systolic hypertension is a definite risk factor for cardiovascular morbidity and mortality independent of diastolic elevation. These complications include coronary artery disease, stroke, and cardiac failure [23] Raised SBP leads to an increase in myocardial oxygen consumption with an enhanced rise of an acute coronary event, lowering of SBP, and thus might be

advantageous especially in hypertensive with ischemic heart disease. [24] In the present study, lowering of SBP with a combination of amlodipine and lisinopril will be beneficial. [28]

Dihydropyridine type of calcium channel antagonists such as nifedipine cause acute diuresis and natriuresis [26] resulting in long lasting loss of sodium and water.[29] This effect is also likely to be present with amlodipine.[28] Loss of sodium and water leads to activation of the renin angiotensinaldosterone system, after treatment with dihydropyridine calcium antagonists, reflecting an increase in circulating concentrations of angiotension II. These effects are likely to offset partly the blood pressure lowering effect of dihydropyridines.[28] Addition of an ACE inhibitor blocks the rise in angiotensin II activity and thus potentiates the effect of calcium channel blockers on blood pressure. ACE inhibitors may also potentiate the action of dihydropyridines by buffering the baroreflex mediated increase in heart rate secondary to vasodilatation due to calcium channel blockers or by indirectly inhibiting the sympathetic nervous system.[19] Amlodipine and lisinopril monotherapy produced a similar fall in blood pressure in our study but a greater blood pressure lowering effect was noticed with the combination of the two drugs and this result consistent with other study[19].Morgan and Anderson reported a higher blood pressure lowering effect with the combination of low doses of enalapril and felodipine.[6]

Short acting dihydropyridines are known to produce reflex tachycardia. In the present study, amlodipine monotherapy did not produce any tachycardia, particularly in a standing position. The ACE inhibitor captopril, in combination, effectively blocked nifedipine induced tachycardia. [18] This results are consistent with the report demonstrated by Cappuccio *et al* [28]

Also our results clearly confirm the significant elevation in the level of HDL-C with amlodipine and greater elevation with combination, this effect could be related to the fact that Oxidized lipid and calcium regulatory abnormalities appear to play important roles in early atherogenesis secondary to cholesterol enrichment of the cell membrane in endothelial and arterial smooth muscle cells (SMCs). [29] However, the link between the two is poorly understood. Amlodipine has membrane-modifying and antioxidant actions at the cell membrane level in addition to its classical calcium channel blocking properties. These multiple pharmacologic actions may explain the cellular mechanisms of the atheroprotective effects of amlodipine in spontaneous atherogenesis and in accelerated atherosclerotic syndromes. Amlodipine inhibits the cholesterol-induced increase in calcium permeability in SMCs, and has been shown to repair abnormalities in SMC membrane structure. [30] Recent data have also demonstrated that amlodipine has a marked antioxidant action in membrane bilayers enriched with polyunsaturated fatty acids. [31,32]

Concerning the reduction in pulse rate observed with amlodipine and combination, this may be due to many factors related to the patients like: dietary restriction, respiratory disease especially viral infection associated with fever, thin and tall patients, athletes patients, drinking tea and coffee, eating heavy meal, and environmental factors. In addition the effect of combination on serum urea and creatinine was of no clinical importance because the increase occurs within the normal range and is possibly related to the patient rather than the treatment given in this study.

We concluded that combination was better to be used in the treatment of hypertension due to many reasons which includes:

Effectiveness of monotherapy limited by stimulation of counter-regulatory mechanisms, effective blood pressure control seen in only 50% of patients on monotherapy; combination therapy results in a much higher responder rate (>80%) and blood pressure goals difficult to attain with monotherapy in patients with diabetes or target organ damage[33,34].

Calcium channel blockers (CCBs) have been suggested as a deterrent for cardiovascular diseases and atherosclerosis, and their antiatherogenic effects have been described in patients with coronary artery disease.[35] A variety of studies, performed in humans and animals, have indicated that CCBs can influence the natural progression of atherosclerosis.[36,37]

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