Original Article

Comparative Study of Efficacy and Safety of Amlodipine plus Rosuvastatin Combination Therapy versus Amlodipine Monotherapy in Patients with Hypertension and Dyslipidaemia

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ABSTRACT

Background: Despite the effectiveness of lipid-lowering as well as antihypertensive medicines in achieving desired levels, the proportion of patients with well-controlled blood pressure remains low. Low compliance is typical in patients having both disorders because many need long-term medication and remain undiagnosed for an extended period of time until consequences from both diseases develop. This study was conducted to compare the efficacy and safety of amlodipine + rosuvastatin combination therapy versus amlodipine monotherapy in patients with hypertension (HTN) and dyslipidaemia.

Methods: 100 patients with HTN and dyslipidaemia were randomise into Group R + A (receiving combination of rosuvastatin (20 mg) plus amlodipine (10 mg) once daily) and Group A (receiving Amlodipine (10 mg) once daily). All patients were requested to attend the facility at 1- and 3-months following randomization to evaluate the efficacy and safety. Outcome measures such as mean SBP, Mean DBP from baseline, LDL-C, total cholesterol (TC), triglyceride and HDL from baseline to 1 month and 3 months were compared using unpaired t-test.

Results: SBP in group A + R was significantly lesser (132.49 ± 7.61) as compared to group A (136.68 ± 7.98) (p=0.0085). There was significantly greater improvement in lipid profile in group A + R as compared to group A. However, there was also some slight improvement with amlodipine monotherapy. There was no significant difference between group A + R and group A with respect to ADRs.

Conclusion: The single-pill FDC "Rosuvastatin-Amlodipine" constitutes a sensible combination of two safe, well-tolerated, evidence-based, and effective medications to treat two major risk factors, such as hypertension and hypercholesterolemia.

Keywords: Rosuvastatin, Amlodipine, Hypertension, Dyslipidaemia.

INTRODUCTION

Cardiovascular diseases (CVD) continue to be the primary cause of morbidity and death worldwide, with a significant influence on global health. [1]

In light of this, a great deal of work has been done in recent decades to develop and expand efficient preventive measures with the goal of lowering the financial burden of CVD through "National Healthcare Systems", Academic Societies, as well as medical professionals in their clinical practices.

The monitoring and treatment of cardiovascular risk on a spectrum, which redefines the therapeutic objectives for every person depending upon their anticipated global risk profile, is the foundation for present cardiovascular disease preventive techniques. Patients frequently need to take many medications to meet treatment aims since the main cardiovascular risk factors—dyslipidaemia, diabetes, and hypertension—cluster together in the same patient. [2]. Furthermore, the risk of cardiovascular disease rises exponentially with the presence of numerous risk factors (RFs). [3]. An extensive observational study found that compared to non-smoking patients with high elevated blood pressure (BP) with adequate cholesterol levels, the probability of serious cardiovascular events was six times higher in hypertensive men with raised total cholesterol and LDL as well as smoking habits. [4]

It seems rather reasonable to speculate that early preventative management measures based on controlling key RFs may help avoid or at least postpone the progression of organ damage as well as may lessen the elevated level of cardiovascular risk, supported by a variety of evidence-based studies. [5]

Despite the effectiveness of lipid-lowering as well as antihypertensive medicines in achieving desired levels, the proportion of patients with well-controlled blood pressure remains low. Just 9% of hypertensive individuals with dyslipidaemia met the goal BP as well as lipid profile levels in one research.[6] A portion of the reason for this less-than-ideal state could be low compliance. [6] Low compliance is typical in patients having both disorders because many need long-term medication and remain undiagnosed for an extended period of time until consequences from both diseases develop. Moreover, complicated treatment plans and polypharmacy are associated with lower compliance.

[7]. Low compliance raises the risk and death of CVD, causing an annual economic cost to rise worldwide. [7, 8, 9]

Prior research has demonstrated that integrated pharmacotherapy of hypertension (HTN) and dyslipidaemia, as opposed to independent management, tends to lower the risk of CVD-related events. [8, 10] These findings have highlighted in clinical practice the significance of multimodal intervention with regard to CVD risk factors. [11–13]

These earlier researches have shown the safety and effectiveness of atorvastatin plus amlodipine combined in a single pill for hypertensive patients along with dyslipidaemia. Therefore, the FDC is now commercially available for use in actual clinical settings. [14–16] Nevertheless, only a few research has been done on rosuvastatin single-pill combinations, despite it being one of the most effective statins for patients with dyslipidaemia. This study was conducted to compare the efficacy and safety of amlodipine + rosuvastatin combination therapy versus amlodipine monotherapy in patients with HTN and dyslipidaemia.

MATERIALS AND METHODS

This was a randomized controlled trial with parallel 1:1 allocation conducted on patients of hypertension with dyslipidaemia visiting out-patient Department of General Medicine of a tertiary care hospital of eastern India from January 2024 to June 2024. Informed consent was taken from patients of HTN with dyslipidaemia as per recommendations of GCP and declaration of Helsinki.

Sample Size: With 22.82 mmHg mean reduction of SBP in amlodipine + rosuvastatin group as compared to 15.89 in amlodipine group with SD of 10 as per previous study [17], minimum sample size required to achieve 90% power with 0.05 alpha value was found to be 88. So, 100 patients were randomized into two groups to cope up with expected attrition rate of 10%.

Inclusion Criteria:

- Patients of either gender with age more than or equal to 19 years
- Patients with diagnosis of hypertension as per JNC 8 guidelines with SBP between 140-159 mmHg and DBP between 90-99 mm Hg.[18]
- Patients with dyslipidaemia as per AHA/ACC guidelines with borderline high LDL-C between 130-159 mg/dL and triglyceride between 150-199 mg/dL.[19]

Exclusion Criteria:

- Patients with difference in BP on both arms
- Patients with secondary hypertension
- Patients with history of hypersensitivity reaction to amlodipine or rosuvastatin
- Patients with coronary artery disease, ischemic stroke or valvular heart disease

Patients who met the requirements for randomization were eventually recruited and divided into one of two treatment groups at random using web generated random numbers following a wash-out/run-in period:

Group R + A: combination of rosuvastatin (20 mg) plus amlodipine (10 mg) once daily

Group A: Amlodipine (10 mg) once daily

In addition to being instructed to preserve adherence to medicine of at least 80% at each visit throughout the research, all patients were requested to attend the facility at 1- and 3-months following randomization to evaluate the efficacy and safety.

Outcome Measures:

- Mean SBP from baseline to 1 month and 3 months
- Mean DBP from baseline to 1 month and 3 months
- LDL-C, total cholesterol (TC), triglyceride and HDL from baseline to 1 month and 3 months

Patients were told to come to the study's location one and three months after being randomly assigned in order to have blood pressure checked and undergo laboratory testing. The participants in the trial were told to take their blood pressure every day. By gathering the adverse event (AE) data and examining vital signs, diagnostic tests, ECG, as well as results of physical exams at every visit, we evaluated the level of safety. A comparison was made between the treatment groups regarding adverse drug reactions. Furthermore, a comparison was made between the prevalence of myopathies and the percentage of patients whose serum aSGOT or SGPT levels were twice in succession more than 3 times above the threshold of normal.

Statistical Analysis:

Data from patients with HTN and dyslipidaemia were presented in tabular form using Microsoft Excel 365 and transferred to SPSS version 24 for further statistical analysis. Continuous data such as age, BMI, SBP, DBP, LDL, TC, TG, and HDL were expressed as mean ± SD (standard deviation). Statistical significance of difference in continuous data between groups was evaluated by unpaired t test. Categorical data, including gender, and adverse events were reported as percentages and frequencies and then compared by chi-square or fisher's exact test. A p-value of less than 0.05 was taken as cut-off for statistical significance.

RESULTS

In this randomised controlled patients, 50 patients each in group A + R and group A completed 3 months of follow-up.

Table 1: Comparison of Baseline Demographic and Clinical Characteristics between Group A + R and Group A

Parameter	Group A+ R (n = 50)	Group A (n = 50)	P-Value
Age in years (mean ± SD)	60.51 ± 9.86	63.53 ± 10.85	0.1484*
Gender (n) Male Female	 29 21	 26 24	 0.6879**
BMI in kg/m^2 (mean ± SD)	25.74 ± 2.25	26.18 ± 2.47	0.3540*
Duration of Hypertension in months (mean ± SD)	111.45 ± 12.64	114.66 ± 13.35	0.2199*
Duration of Dyslipidaemia in months (mean ± SD)	69.78 ± 7.08	73.53 ± 8.15	0.2545*

*Unpaired t-test **Fisher's Exact Test

Most of the patients were males of age group 50-70 years. There was no significant between group A + R and group A with respect to age, gender, BMI, duration of HTN or dyslipidaemia (p>0.05).

Table 2: Comparison of Blood Pressure between Group A + R and Group A

Parameter	Time	Group A+ R (n = 50)	Group A (n = 50)	P-Value (Unpaired t Test)
Systolic Blood Pressure	Baseline	154.34 ± 9.48	151.46 ± 9.38	0.1300
	1 Month	143.75 ± 8.37	147.64 ± 8.49	**0.0231**
	3 Months	132.49 ± 7.61	136.68 ± 7.98	**0.0085**
Diastolic Blood Pressure	Baseline	93.57 ± 7.13	91.7 ± 8.61	0.2397
	1 Month	91.24 ± 7.02	90.05 ± 8.43	0.4449
	3 Months	86.53 ± 6.87	88.94 ± 8.09	0.1116

SBP in group A + R was significantly lesser (132.49 ± 7.61) as compared to group A (136.68 ± 7.98) (p=0.0085).

Table 3: Comparison of Lipid Profile between Group A + R and Group A

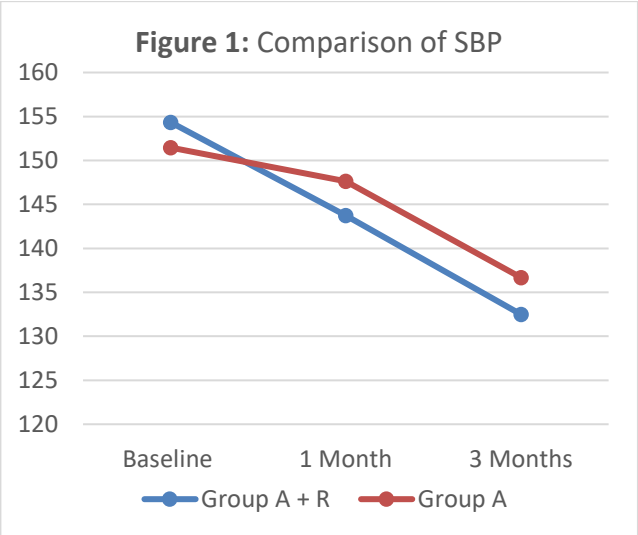
Parameter	Time	Group A+ R (n = 50)	Group A (n = 50)	P-Value (Unpaired t Test)
LDL	Baseline	151.82 ± 17.16	153.05 ± 14.55	0.6999
	1 Month	140.97 ± 13.23	151.39 ± 14.28	**0.0002**
	3 Months	123.85 ± 11.55	148.37 ± 14.13	**<0.0001**
TC	Baseline	214.49 ± 21.02	219.82 ± 20.14	0.1985
	1 Month	198.56 ± 19.82	215.32 ± 19.96	**0.0001**
	3 Months	173.42 ± 17.96	206.56 ± 19.17	**<0.0001**
TG	Baseline	177.35 ± 18.57	180.47 ± 17.49	0.3892
	1 Month	165.73 ± 15.34	177.91 ± 17.42	**0.0003**
	3 Months	147.28 ± 13.23	174.06 ± 17.33	**<0.0001**
HDL	Baseline	39.03 ± 5.45	37.05 ± 7.53	0.1352
	1 Month	41.54 ± 4.19	38.21 ± 6.82	**0.0041**
	3 Months	44.53 ± 4.06	40.26 ± 5.53	**<0.0001**

There was significantly greater improvement in lipid profile in group A + R as compared to group A. However, there was also some slight improvement with amlodipine monotherapy.

Table 4: Comparison of Adverse Drug Reactions between Group A + R and Group A

ADR	Group A+ R (n = 50)	Group A (n = 50)
Peripheral Oedema	3	1
Headache	1	2
Dizziness	1	0
Total	5	3

There was no significant difference between group A + R and group A with respect to ADRs. No groups experienced ADRs during the trial period that resulted in stopping the study drug and/or death. No patients had myopathy or blood levels of SGOT as well as SGPT more than three time above the threshold of normal for two consecutive tests. Clinically significant alterations in vital signs or an electrocardiogram were not observed in any of the individuals.



DISCUSSION

In this randomised controlled trial, the rosuvastatin + amlodipine combination showed better BP-lowering as well as lipid-modulating effects in patients with hypertension and dyslipidaemia than did amlodipine alone. Additionally, the combination's target level accomplishment rate was higher than that of monotherapy while remaining tolerable with respect to of safety.

There have been numerous attempts to produce a FDC for the pharmacotherapy of different diseases, because the administration of a FDC instead of the usage of a regimen containing free-drug ingredients may enhance efficacy by enhancing compliance. [20] According to a prior meta-analysis, the FDC lowered the probability of non-compliance by 26% when compared with a regimen including free-drug ingredients. [20] The safety and effectiveness of co-administering amlodipine plus atorvastatin in patients with hypertension and dyslipidaemia have been well established, and single-pill combinations of these two medications have been proven to enhance compliance, leading to a decrease in CVD events. [21]

One of the most effective statins, rosuvastatin is "a 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor" that is rapidly absorbed, quickly achieves peak plasma concentrations, possesses a long half-life, and is utilized widely over the world.[22] Unlike atorvastatin plus amlodipine studies, none that we are aware of have examined the use of rosuvastatin + amlodipine in combination therapy for patients with HTN + dyslipidaemia. It's interesting to note that recent reports have shown the safety and effectiveness of a triple combinations consisting of amlodipine along with rosuvastatin.[23, 24] Since findings on the safety as well as effectiveness of a FDC may not always be favourable, it is still important to establish the safety and efficacy of the double combination comprising rosuvastatin plus amlodipine.[25]

Beyond the potential increase in compliance through pill burden reduction, the precise mechanism by which lipid modification and blood pressure reduction work in concert in the group A + R remains unclear. By lowering oxidative stress, limiting inflammatory reactions, and improving nitric oxide bioavailability, statins are believed to help restore endothelial dysfunction and so somewhat decrease blood pressure.[26] Comparably, in addition to decreasing blood pressure, amlodipine has been shown to have anti-inflammatory and antioxidative stress properties, which may help with lipid management.[27]

It's intriguing that participants receiving amlodipine plus rosuvastatin in this trial experienced a higher drop in blood pressure after one and three months compared to those receiving amlodipine alone. [28]

Studies have shown a little but significant drop in blood pressure, and there has been ongoing interest in the hypotensive effects of statins outside of their ability to lower cholesterol.[29, 30] Still, there is a disagreement that yields inconsistent findings. [31, 32] This is because the majority of trials had small sample sizes and short study durations, and it is challenging to definitively pinpoint the statins' impact on decreasing blood pressure when used in conjunction with concomitant antihypertensive medication. Furthermore, no research has compared the use of rosuvastatin to other statin classes in an effort to control blood pressure.

This study has certain shortcomings as well. The study has some limitations, including a small number of participants and a comparatively short follow-up time. In the end, it is critical to determine whether a more synergistic impact exists and whether this combination preserves the CVD protective benefit that has been demonstrated for each individual treatment. However, the research's design alone made it difficult to establish this effect on CVD; so, more research in this area is required.

CONCLUSION

Combination therapy with amlodipine (10 mg) plus rosuvastatin (20 mg) efficiently and safely decreased blood pressure and low-density lipoprotein (LDL-C) levels in hypertensive individuals with dyslipidaemia. The single-pill FDC "Rosuvastatin-Amlodipine" constitutes a sensible combination of two safe, well-tolerated, evidence-based, and effective medications to treat two major risk factors, such as hypertension and hypercholesterolemia, thereby lowering the burden associated with cardiovascular events. However, it has not yet been widely adopted in clinical practice.

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