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Research Article

TO COMPARE THE EFFICACY AND SAFETY OF RAMIPRIL VERSUS LOSARTAN IN POST-MYOCARDIAL INFARCTION PATIENTS

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ABSTRACT

Objective: Renin–angiotensin–aldosterone system (RAAS) plays an important role in regulating post-myocardial infarction (post-MI) events. Ramipril and losartan act mainly by inhibiting RAAS. This study was designed to compare the efficacy and safety of ramipril against losartan in post-MI patients.

Methods: A total of 100 enrolled patients were divided into two groups A and B of 50 each by computer-generated random numbers. Group A (n=50) patients were given ramipril 1.25–2.5 mg once a day and Group B (n=50) patients were given losartan 25–50 mg once a day. The patients were followed after 0, 1, and 3 months and at 6 months (optional). Efficacy was compared based on the left ventricular ejection fraction (LVEF%) and New York Heart Association class improvement. Safety was compared by considering ADRs, mortality, and biochemical test profile. Data were analyzed using unpaired t-test and Chi-square test. $p<0.05$ was considered to be statistically significant.

Results: The mean LVEF% at 0 month for Group A was 40.6 ± 4.48 and for Group B was 39.6 ± 4.02 (p=0.212). The mean LVEF% at 6 months for Group A was 45.12 ± 4.6 and for Group B was 43.57 ± 4.03 (p=0.11). The most common side effects were headache in Group A and hypotension in Group B.

Conclusion: Both ramipril and losartan are equally efficacious; however, losartan has a better safety profile than ramipril.

Keywords: Left ventricular, Remodeling, Angiotensin.

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INTRODUCTION

Coronary artery disease (CAD) is a major cause of death and disability in developed countries [1]. The 2016 Heart Disease and Stroke Statistics update of the American Heart Association has recently reported that 15.5 million persons ≥20 years of age in the USA have CAD [2], and the overall death rate from CAD was 102.6/100,000 population [3]. In India, the prevalence has increased to 9%–10% in urban populations and 4%–6% in rural populations [4].

Post-myocardial infarction (post-MI) events such as left ventricular (LV) dilatation and remodeling start immediately after acute MI and upregulation of renin–angiotensin–aldosterone system (RAAS) plays an important role in the pathogenesis of LV remodeling in post-MI patients [5]. Successful mechanical reperfusion therapy and current pharmacological treatment can limit cardiac dysfunction and ventricular remodeling in acute MI to some extent [5]. The current modalities of pharmacologic treatment of post-MI are beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) [6].

ACEI and ARBs are considered a breakthrough in the treatment of post-MI patients for reducing mortality and morbidity [7]. Numerous studies have been conducted in the past to compare the efficacy and safety of ACEIs against ARBs, but still, there is no conclusive evidence. Hence, the present study was designed with an aim to compare the efficacy and adverse reaction profile of ramipril versus losartan in post-MI patients.

MATERIALS AND METHODS

It was a prospective, open-label, comparative randomized study and was conducted in a total of 100 (n=100) patients. Patients were enrolled as per the inclusion and exclusion criteria. Patients underwent a thorough clinical examination including history for any ongoing disease or drug intake, vital signs, and systemic examination. Informed consent was taken from the patients.

The inclusion criteria were 7 days post-MI patients of age between 20 and 75 years of either gender with a history of ST elevation on electrocardiogram and LV dysfunction with the LV ejection fraction (LVEF) ≤45%. Pregnant and lactating women, patients with known hypersensitivity to angiotensin receptor inhibitors and ARBs, known cases of angioedema, renal artery stenosis, aortic stenosis, hypertrophic cardiomyopathy, collagen vascular diseases, and renal dysfunction with serum creatinine >1.5 mg/dl were excluded.

After signing the written informed consent, 100 patients were enrolled. The enrolled patients were divided into two groups A and B by computer-generated random numbers. Both the groups consisted of 50 patients each. Group A (n=50) patients were given ACEI (ramipril) 1.25–2.5 mg once a day and Group B (n=50) patients were given ARB (losartan) 25–50 mg once a day. The patients were followed after 0, 1, and 3 months, and 6 months (optional). The baseline clinical characteristics recorded were systolic and diastolic blood pressure (mmHg), heart rate per min, respiratory rate per min, and peripheral capillary oxygen saturation (SpO_2%), at the time of enrollment for every patient and were reevaluated during follow-up as needed. Efficacy was compared based on the primary parameters and safety based on the secondary parameters.

Primary parameters were LVEF and New York Heart Association (NYHA) classification. Secondary parameters were adverse drug reactions (ADRs) which were spontaneously recorded; renal function tests which included blood urea nitrogen, serum creatinine, sodium, and potassium, and the number of deaths.

Data were analyzed using unpaired t-test and Chi-square test. p<0.05 was considered to be statistically significant.

RESULTS

The mean age of patients was 56 ± 10.89 years in Group A and 55.92 ± 9.53 years in Group B. In Group A, there were 39 males and 11 females and Group B also had 39 males and 11 females. The mean weight of patients was 63.16 ± 5.72 kg in Group A and 63.5 ± 5.78 kg in Group B. The demographic baseline characteristics have been shown in Table 1.

There was no significant difference in the demographic profile in both the groups (p>0.05).

The baseline clinical characteristics of patients in both the groups are given in Table 2.

The mean LVEF% at 0 month for Group A was 40.6 ± 4.48 and for Group B was 39.6 ± 4.02 (p=0.212). The mean LVEF% at 6 months for Group A was 45.12 ± 4.6 and for Group B was 43.57 ± 4.03 (p=0.11) (Table 3). The mean LVEF% was slightly higher in Group A as compared to Group B at baseline and 6 months; however, it was not statistically significant (p>0.05). There was an increasing trend in LVEF% in both Group A and Group B with respect to time, but the difference in LVEF% between the two groups at 0 and 6 months was comparable (p>0.05).

The NYHA classification of study participants in both the groups is depicted in Table 4. Functional outcome in both the groups was comparable (p>0.05). At baseline in Group A, 72% of the study participant was in Class 1, and in Group B, 68% of the study participant was in Class 1. There was no significant difference in the functional outcome in both the groups (p=0.663) at baseline. At 1 month, 3 months, and 6 months, all the study participants of both the groups were in Class 1. There was no significant difference in NYHA classification between the two groups.

ADR monitoring was done for both Group A and Group B (Table 5). There was no statistically significant difference in ADR between two groups (p>0.05) except headache (p<0.05). In the study Group A, 12% of patients reported headache, whereas in the study Group B, no patient reported headache so the incidence of headache in the study Group A was significantly higher as compared to B (p=0.027). There was no statistically significant difference in the incidence of dry cough, hypotension, abnormal kidney function, and hyperkalemia between two groups (p>0.05). Seven patients of Group A and six patients of Group B left the study due to the side effects. There was mortality of three patients within 6 months.

Table 1: Demographic baseline characteristics

Demographic characteristic	Group A (%)	Group B (%)	Total (%)
≤40 years	4 (8.00)	3 (6.00)	7 (7.00)
41–50 years	12 (24.00)	11 (22.00)	23 (23.00)
51–60 years	16 (32.00)	24 (48.00)	40 (40.00)
61–70 years	18 (36.00)	12 (24.00)	30 (30.00)
Mean age (y)	56±10.89	55.92±9.53	55.96±10.18
F; Female	11 (22.00)	11 (22.00)	22 (22.00)
M; Male	39 (78.00)	39 (78.00)	78 (78.00)
Mean weight (kg)	63.16±5.72	63.5±5.78	63.33±5.73

Table 2: Baseline clinical parameters of study participants

Clinical parameters	Group A	Group B	p
SBP (mmHg)	112.48±9.46	116.8±11.81	0.097*
DBP (mmHg)	75.28±5.75	76.12±6.61	0.51*
HR/min	83.24±10.68	84.1±10.59	0.895*
Respiratory rate/min	20.72±2.17	20.64±1.48	0.616*
SpO_2%	98.56±0.5	98.7±0.46	0.149*

*p>0.05. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate

DISCUSSION

In our study, the mean age of patients in both the groups was comparable (p>0.05) with most of them being in 51–70 years age group with confirmed acute MI. In the ELITE study [8], patients were 65 years or more, in the OPTIMAAL study [9], patients were 50 years of age or older (mean age 67.4 years [standard deviation 9.8]). Similar results were seen by Kumar *et al*. [10].

The sex distribution in both the groups was comparable, with 78% of males and 22% of females and mean weight of 63.33 ± 5.73 kg. Women are less susceptible to coronary heart disease and other atherosclerotic diseases as compared to men [11].

The baseline clinical characteristics studied were systolic and diastolic blood pressure (mmHg), heart rate per min, respiratory rate per min, and SpO_2%. The difference of parameters between the two groups was not statistically significant in our study. Similar results were seen in other studies also where no difference in outcome was seen compared with their baseline clinical parameters. Garg and Yusuf [12] and Flather *et al*. [13] found that the benefits of treatment on all outcomes were independent of age, sex, and baseline use of diuretics, aspirin, and beta-blockers.

Mean LVEF% in our study was 40.1 ± 4.26. A follow-up of 3–6 months was done. All the patients were in Class 1 and 2 NYHA. A stringent inclusion criterion of LVEF% <45 was being followed in our study. Other studies had slightly different criteria. Køber *et al*. [14], in the Trandolapril Cardiac Evaluation trial, randomized post-MI patients with an LVEF of 35% or less with a follow-up of 24–50 months. Yusuf *et al*. [15] excluded patients with an LVEF <40% or a history of chronic heart failure. In his study, subjects were randomized to treatment with ramipril or placebo for an average of 5 years. Pitt *et al*. [8] in the ELITE study compared the safety and efficacy advantages of losartan with captopril in the treatment of older heart failure patients. A number of 722 ACEI-naive patients (aged 65 years or more) with NYHA Class II-IV heart failure and ejection fractions of 40% or less were followed for 48 weeks. In a study by Pfeffer *et al*. [16], patients were randomized

Table 3: Left ventricular ejection fraction (%) (mean±standard deviation) in groups at baseline and 6 months

Follow-up interval	LV%–EF%		p
	Group A	Group B	
0 month	40.6±4.48	39.6±4.02	0.212
6 months	45.12±4.6	43.57±4.03	0.11

*p<0.05 as compared to 6 months. LV: Left ventricular, EF: Ejection fraction

Table 4: New York Heart Association classification of study participants

Functional outcome	Group A (%)	Group B (%)	Total (%)	p
0 month				
Class 1	36 (72.00)	34 (68.00)	70 (70.00)	0.663
Class 2	14 (28.00)	16 (32.00)	30 (30.00)	
1 month				
Class 1	49 (100.00)	44 (100.00)	93 (100.00)	-
Class 2	0 (0.00)	0 (0.00)	0 (0.00)	
3 months				
Class 1	41 (100.00)	42 (100.00)	83 (100.00)	-
Class 2	0 (0.00)	0 (0.00)	0 (0.00)	
6 months				
Class 1	41 (100.00)	42 (100.00)	83 (100.00)	-
Class 2	0 (0.00)	0 (0.00)	0 (0.00)	

Table 5: Adverse drug reactions of study subjects

ADR	Group A (%)	Group B (%)	Total (%)	p
Dry cough	3 (6.00)	0 (0.00)	3 (3.00)	0.242
Angioedema	0 (0.00)	0 (0.00)	0 (0.00)	-
Hyperkalemia	0 (0.00)	1 (2.00)	1 (1.00)	1.000
Hypotension	3 (6.00)	3 (6.00)	6 (6.00)	1.000
Dizziness	0 (0.00)	0 (0.00)	0 (0.00)	-
Postural hypotension	0 (0.00)	0 (0.00)	0 (0.00)	-
Nausea	0 (0.00)	0 (0.00)	0 (0.00)	-
Vomiting	0 (0.00)	0 (0.00)	0 (0.00)	-
Headache	6 (12.00)	0 (0.00)	6 (6.00)	0.027
Abnormal kidney function	1 (2.00)	2 (4.00)	3 (3.00)	1.000
Diarrhea	0 (0.00)	0 (0.00)	0 (0.00)	-
Vasculitis Henoch-Schonlein purpura	0 (0.00)	0 (0.00)	0 (0.00)	-
Vertigo	0 (0.00)	0 (0.00)	0 (0.00)	-
Impotence	0 (0.00)	0 (0.00)	0 (0.00)	-

ADR: Adverse drug reaction

with an LVEF ≤40% to placebo or captopril 3–16 days post-MI and were followed for a mean of 42 months.

Our results showed a significant improvement in LVEF% and NYHA class in both the groups ($p<0.0001$), but not significantly different from each other. In our study, ramipril and losartan attenuated progressive increases in LV dilation and hypertrophy in patients with LV dysfunction, irrespective of the patient's symptomatic status.

In comparison, both the drugs were found to be equally effective. Hence, an efficacy advantage of either drug could not be established. Other studies in the past such as OPTIMAAL and VALIANT trials also could not establish the efficacy advantage of ARBs over ACEIs [9,16,17].

ACEIs, but not ARB, prevent bradykinin degradation and allow it to accumulate, leading to the known side effects of ACEI therapy such as cough, rash, and angioedema [18]. Thus, the most common and noticeable side effect of dry cough is common with ACEI therapy and minimal with ARBs. In our study, dry cough was seen only in patients treated with ramipril and not with losartan. Side effects such as a mild headache, hypotension, and abnormal kidney function tests were seen in few of the ramipril-treated patients. Other known side effects of ramipril such as angioedema, dizziness, nausea, vomiting, diarrhea, vasculitis Henoch-Schönlein purpura, vertigo, and impotence were not seen in our study. Losartan, the first ARB that was approved for clinical use, has been associated with a low incidence of cough, similar to that of the diuretic hydrochlorothiazide, in patients with a history of ACEI-induced cough [19]. Numerous comparative trials have been performed, demonstrating the lower incidence of cough associated with several ARBs compared to that with ACEIs [20]. In our study, no patient treated with losartan reported cough as a side effect. Side effects such as hypotension, abnormal kidney function tests, and hyperkalemia were seen in few of the losartan-treated patients. Seven patients left the study due to side effects of ramipril. OPTIMAAL and VALIANT trial showed similar results in terms of side effects and discontinuations from the study [9,16,17].

In our study, serum potassium, sodium, creatinine, and BUN levels were regularly monitored. Mild hyperkalemia was reported in few patients on losartan but not in ramipril group. Other biochemical parameters were in the control range. No alarming values were reached for any patient in the study. An improvement in the biochemical values was seen in both ramipril- and losartan-treated patients on regular follow-ups.

Due to the effects on RAAS, the use of ACEI and ARBs can be associated with hyperkalemia, especially in patients with chronic renal sufficiency. Up to 10% of the patients may experience at least hyperkalemia [20]. However, Hameed *et al*. [21] noted no side effect with losartan as compared to amlodipine. These ADRs can be minimized by creating awareness among the professionals [22].

Mortality and the number of patients leaving the study were comparable in both ramipril- and losartan-treated groups. There was no direct mortality due to side effects of drugs. Patients left the study due to the side effects, particularly mild headache and cough. Fewer patients in the losartan group (excluding those who died) discontinued study due to adverse effects in other studies such as ELITE II, VALIANT, and OPTIMAAL trials [9,16,17]. Further studies entailing long follow-up and more patients with a different combination of drugs may be required to arrive at a definitive conclusion and to know the long-term side effects of the drugs.

The main strengths of this study were the completeness of the investigations in terms of baseline and 6-month follow-up. Although the MI diagnosis was not validated, LVEF and NYHA class were taken into account. Detailed information about important risk factors such as smoking and obesity and family history was obtained. This study did analyze the efficacy and side effects of ACEIs and ARBs in the early treatment post-MI, contributing to the data in other different studies.

CONCLUSION

Both ramipril and losartan are equally efficacious; however, losartan has a better safety profile than ramipril; therefore losartan can be preferred in certain patients.

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AUTHORS' CONTRIBUTIONS

1st Author – Guarantor, data acquisition, from inception till end of the study
2nd Author – Concept and design of study, clinical study, final approval of the version
3rd Author – Concept and design of study, clinical study, final approval of the version
4th Author – Concept and design of study, clinical study.
5th Author – Concept and design of study, clinical study, final approval of the version.

CONFLICTS OF INTEREST

None declared.

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