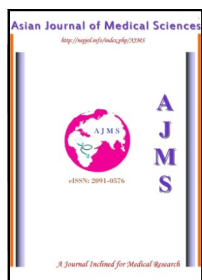


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Age Dependent Efficacy of Ace Inhibitors Among Chinese Cardiovascular Patients During Hospitalization Phase

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Abstract

Objective: Cardiac failure is a global burden among cardiovascular diseases, and major cause of morbidity and mortality especially among elderly age group. Angiotensin Converting Enzyme (ACE) inhibitors, remained the choice of treatment as they inhibit the renin angiotensin aldosterone system along with reduction in levels of pro-inflammatory cytokines, both of them are key factors in progression and complications of heart failure. The aim of this study was to rule out the effect of aging and efficacy of ACE inhibitor, Captopril, among Chinese cardiovascular patients with acute myocardial infarction (MI) during the hospitalization phase of therapy.

Material & Methods: Randomized control trial at hospital of Tongji Medical College Wuhan, China over a period of more than 1 year from April 2009 till July 2010 recruiting patients in two stages. A total of 260 patients with mean age 65±8 years were recruited. All suffered from first time myocardial infarction and arrived in Cardiac emergency within 72 hours of the event. The participants were then randomly divided in study and control groups which were then further classified in sub-groups depending upon their age. Study group received ACE inhibitor Captopril in addition to standardized therapy while control group just received the conventional therapy for the event. Statistical analyses were done to formulate the correlation between multi-variables.

Results: Participants were divided in Study group (N=150) (A and C, Young and Old) and the control group (N=110) (B and D, Young and Old). Survival rate was better among elderly on captopril in comparison to younger ones during the hospitalization. The Systolic blood pressure among study group was significantly lower than control group (132.9±16.3mmHg/84.7 ±9.1mmHg vs. 147.1±17.4mmHg/85.1 ±10.9mmHg, P<0.05). Patient's survival was statistically significant with respect to age (P<0.001).

Conclusion: Treatment with Captopril is definitely associated with improved short as well as long term cardiac prognosis and markedly. Captopril therapy is associated with improved long term prognosis and reduced cardiac mortality during the hospitalization phase of the therapy and recovery period. But the most significant finding is that the increased survival after taking Captopril was higher in elderly patients than in younger patients. ACE inhibitors like Captopril in proper dosage play a real vital beneficial role among elderly patients as compared to the younger ones, but still there is need to recruit a large cohort in different ethnic groups with different genetic makeup.

Key Words: Myocardial infarction (MI); Ace-inhibitor; Aging

1. Introduction

Cardiac failure, a major cause of morbidity and mortality all around the world, is an important public health challenge in the upcoming era of health care system.^{1,2} Right after the myocardial infarction, the neuro-endocrine system gets activated. Left ventricle dilatation is linked to increase in size of infarcted zone as expansion and the remodeling of the ventricle.^{3,4} Angiotensin II on one hand leads to sodium retention and hypertension with negative impact over pumping action of

heart⁵, and on the other hand leads to pro-inflammatory actions as determined by raised levels of C-reactive proteins. In heart failure patients, high sensitivity C-reactive protein is associated with acute decompensation of heart failure and associated complications.^{6,7} Long-term Angiotensin converting enzyme (ACE) inhibitor therapy usually improve the outcome of cardiovascular disease specially acute myocardial infarction by altering the mechanism of infarct expansion and left ventricular remodeling which may result in left ventricular dilatation and activation of the neuro-endocrine system.⁸⁻¹¹

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Among Heart failure patients with left ventricular

dysfunction, chronic blockade of the renin-angiotensin system is a definitive therapeutic option in improving both the mortality and morbidity with a normal anatomy.¹² Treatment of cardiac failure patients with ACE inhibitors accompanied by acute ischemic event leads to an improvement in prognosis¹³, with additional benefits of limited adverse ventricular remodeling and reduced incidence of recurrent infarction.^{14,15} ACE inhibitor therapy among patients of myocardial infarction has survival benefits as well. Primary mechanism has been proved to alter the change in volume of the left ventricle and by improving its performance during systole.^{8,13,16} ACE inhibitors are the first-choice of therapy to improve the prognosis among Cardiac failure patients especially complicated by myocardial infarction.² Also, angiotensin receptor blockers act as being beneficial among cases of systolic heart failure. Captopril can remarkably improve the diastolic filling so as to decrease the left ventricular load after myocardial infarction.¹⁷ It also limit the decline in function of adjacent non-infarcted areas which is an important determinant of LV remodeling.¹⁸ Captopril causes acute selective enhancement of LV relaxation without disturbing the coronary blood flow, possibly through an endogenous bradykinin and nitric oxide neuro-endocrine pathway¹⁹ thus exhibiting many beneficial effects.

Left ventricular dyssynchrony is directly linked with the progression of heart failure. It is a major factor contributing in the reduction of ejection fraction, because of insufficient pumping along with energy expenditure, thus leading to poor outcome.^{20,21} Mechanical dyssynchrony is strongly influenced by hemodynamic changes, Left Ventricular heterogeneity and myocardial fibrosis.²²

Cardiac rehabilitation phase is the key in determining the future prospects, and making a probability about upcoming cardiac problems and among patients with acute myocardial infarction, it is usually divided primarily to hospitalization phase (phase 1-inpatient) and follow-up phase (phase 2 and 3 Phase 2-Outpatient Programme (from hospital discharge to 12 weeks). Phase 3-Maintenance Programme (ongoing, to maintain health gains, cardiac club) of rehabilitation lasting usually up to 6 months from the day of infarction.²³

Among patients with first time myocardial infarction event, age may be a powerful independent indicator of mortality rate within the hospital, age-related increase in the mortality rate cannot be explained by large

infarcts.²⁴⁻²⁶ Efficacy of Ace inhibitors has already been proven among patients of acute myocardial infarction, but there is very little data available regarding its efficacy among various age groups and during different phases of cardiac rehabilitation.^{18,27} As most of conclusions about the effects of ACE-Inhibitors have been drawn from animal models on ischemic events of the heart on acute basis.^{3,13-15}

So, the aim of this study was to evaluate the clinical efficacy of ACE inhibitors in various age group cardiovascular patients after acute myocardial infarction with primary focus of its benefits during the hospitalization phase of early rehabilitation.

2. Material and Methods

A randomized control trial was carried out at the teaching hospital of Tongji Medical College Wuhan, China. This union hospital is a tertiary teaching hospital equipped with specialized cardiology department with all the modern facilities. Study duration was more than 1 year from April 2009 till July 2010 recruiting patients in two stages. In first stage, we recruited 100 patients in first 6 months, and then later recruited 160 more patients till July 2010, and recruiting more and more patients to gather big cohort so as to more authenticate the results. A total of 260 patients were recruited. Mean age 65±8 years and 55% were males. All the participants of the study were cases of first time myocardial infarction and arrived in Cardiac emergency within 72 hours of the event. All received admissions, with acute myocardial care, given conventional infarction treatment like heparinization, thrombolysis, and B-blockers. Oral aspirin was also given along with antihyperlipidemics in cases of proven obese patients. All the participants were then randomly divided in study and control groups which were then further classified in sub-groups depending upon their age. Study group received ACE inhibitor Captopril in addition to standardized therapy while control group just received the conventional therapy for the event. At the time of admission, Captopril 6.25 mg per orally was given and mainlined at a dose of 12.5-25 mg tds, while monitoring blood pressure. Unstable patients with severe hyper or hypotension were excluded from the study. During the study, patients were continuously monitored in terms of sudden cardiac deaths, congestive cardiac failures, arrhythmias and reinfarction/reperfusion injuries. Variables were defined in terms of hypertension, diabetes mellitus, peak CPK-MB, troponin T levels and Left ventricular ejection fraction. Statistical Analyses

were done by using SPSS 12.0 version and a probability (P) of <0.05 was considered significant.

3. Results

All the participants were divided in Study group (N=150) (A and C, Young and Old) and the control group (N=110) (B and D, Young and Old). Age demarcation was at 60 years, i. e. patients below 60 years were regarded young in sense of myocardial disorders while older than this value were categorized as elderly group.

Table -1: Characteristic of Study participants

No	Result Characteristics	Group A	Group B	Group C	Group D
1	Total No. of Patients (n)	75	55	75	55
2	Hospital Deaths (n)*	2	3	5	19
3	LV Ejection fraction	54.1% ±11.7%	52.9% ±13.2%	55.1% ±13.7%	54.6% ±13.5%
4	Hospital stay (Days)	27 ±11	29 ±10	28 ±12	27 ±11
5	Oral Aspirin	43	21	41	27
6	B-blockers	39	19	34	17
7	Received Thrombolysis	41	24	36	21
8	Artery Patency rate	46.7%	47.3%	47.4%	41.3%

*Hospital deaths were statistically significant with *P <0.05
 A: Young patients receiving Captopril; B: Young patients receiving just standard Therapy; C: Elderly patients receiving Captopril; D: Elderly patients receiving just standard Therapy

The patients were then further subdivided in to younger study group (Group A=75), younger control group (Group B=55), elderly study group (Group C=75) and elderly control group (Group D=55). No participant had any severe extra-cardiac disease manifestation which could affect the prognosis. Patients with hypotension or hypertension (Systolic B.P< 89mmHg was defined hypotension while Systolic B.P> 199 mm Hg and/or Diastolic pressure >119 mm Hg) were excluded. Coronary arterial stenosis (above 65%) was assessed by arteriography. 43 patients in Group A, 21 in Group B, 41 in Group C, and 27 in Group D took oral aspirin (all P>0.05). Moreover, 39 patients in Group A, 19 in Group B, 34 in Group C, and 17 in Group D took oral beta-blockers (all P>0 .05).The results have been summarized in table 1 and 2.

Table -2: Parameters among Study and Control groups

PARAMETERS	CAPTOPRIL (STUDY) GROUP	CONVENTIONAL THERAY (CONTROL) GROUP
No. of Participants	150	110
Sys.B.P (mmHg)	132.9±16.3	147.1±17.4
Mean B.P (mmHg)	136.43	145.78
Standard deviation (S.D)	8.11	11.26
Variance S.D	62.92	102.88
Population S.D	7.68	9.89
Variance Population S.D	63.01	98.84

Hospitalization time remained the same among all the groups on average. The careful analysis of hospital deaths showed statistical significance and is summarized in Table 1. The Systolic blood pressure among patients who were on ACE inhibitor therapy was significantly lower than patients who got the conventional therapy only (132.9±16.3mmHg/84.±9.1mmHg vs. 147.1±17.4mmHg/85.1 ±10.9mmHg, P<0.05).

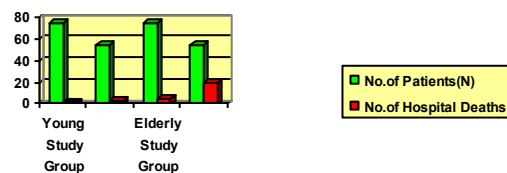


Figure -1: Graphical Data Showing No. of Participants and Hospital Deaths
 Ejection fraction in Group A, B, C, and D were 54.1%±11.7%, 52.9% ±13.2%, 55.1%±13.7% and 54.6%±13.5% respectively. Our results clearly indicated that the survival of patients on Captopril correlated significantly with age (P<0.001) (Fig-1).

4. Discussion

ACE inhibitors like Captopril has an extremely beneficial effect on elderly patients (60-70 years old) during the hospitalization phase of rehabilitation after myocardial infarction as shown by our study. Captopril protects the ischemic and infarcted zone of injured myocardium after the myocardial infarction and markedly enhances the survival of old aged patients.

Inhibitions of pro-inflammatory cytokines have been also observed by Captopril in the past.²⁸⁻³⁰ Captopril not only decreases the levels of angiotensin II, but the potentiated effect is actually by the reduction of cytokines which are not observed among other ACE inhibitors.³¹ It also effect levels of prostaglandins, which are strong inhibitors of cytokines.³² Captopril is also involved in inhibiting the production of TNFα, a factor involved in inflammation.³¹ In heart failure patients, the adrenergic system gets activated quickly both in the heart and systemically.³³

Central sympathetic activity is increased in addition to circulating catecholamine.^{34,35} Main role of Captopril is to relive patients with congestive cardiac failure through inhibition of inflammatory cytokines, especially among patients cachexia superimposing.³⁶

Beta-blockers like metoprolol also enhance its efficacy and beneficial effects. Captopril decreases the fatal life threatening repetitive ventricular arrhythmias and catecholamine levels during acute thrombolytic phase of myocardial infarction providing the evidence that a proper dose of beta-blocker might further help patients taking Captopril in the early hospitalization phase of the recovery among patients with acute myocardial infarction.¹⁴

Treatment with Captopril is definitely associated with improved short as well as long term cardiac prognosis and

markedly. Captopril therapy is associated with improved long term prognosis and reduced cardiac mortality during the hospitalization phase of the therapy and recovery period. But the most significant finding is that the increased survival after taking Captopril was higher in elderly patients than in younger patients.

Also Captopril exerts beneficial effect in reducing the number of complex ventricular arrhythmias in post-myocardial ischemic patients accompanied by left ventricular dysfunction, mediated via alterations in left ventricle remodeling.^{37,38}

The study positively concludes that ACE inhibitors like Captopril in proper dosage play a real vital beneficial role among elderly patients as compared to the younger ones during hospitalization phase of recovery after acute myocardial infarction

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