Original research article

A Prospective, Follow- Up Study in aTertiary- Care Centre Drug Treatments in Post- Myocardial Infarction Arrhythmias

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Abstract

Background: CVD is a major non-communicable disease in India with a high burden of morbidity and mortality. A large proportion of the cardiovascular diseases consist of coronary artery disease (CAD). Acute coronary syndrome (ACS) is an important sub-class of CAD associated with significant mortality. Most of the deaths during the peri-infarction period are due to cardiac arrhythmias, a condition for which reliable evidence from India is lacking. Assessment of the patterns and management of cardiac arrhythmias in the Indian subcontinent thus becomes essential to quantify, and more importantly, to prevent the high mortality associated with the disease.

Objectives: The objectives of our study were: a) To determine the demography, presentation, patterns, treatments of acute myocardial infarction (AMI) patients with arrhythmia.

Methods: A prospective, follow-up study over Two years at the Department of Cardiology, Jay Prabha Medanta super Speciality Hospital, Patna. We recruited 202 patients with AMI. Of these, 102 developed arrhythmia and 100 did not develop arrhythmia. Patients with AMI and arrhythmia were followed-up at 1 month and 6 months after discharge. Data on demography, patient presentation, patterns of arrhythmias, treatments and outcomes were collected. Baseline data were summarizedusing descriptive statistics.

Conclusion: In this study, we described the demography of AMI patients who developed arrhythmias, patterns of arrhythmias and their treatment in a tertiary-care hospital in India. We found out that about half the patients with AMI develop arrhythmia as a complication. Most of the patients received pharmacotherapy for the treatment of arrhythmias, few received non-pharmacological measures in addition to drug therapy. Revascularization is known to be the best treatment for infarct-related complications.

Keywords: ACS, CAD, CVD, AMI, Arhythmias.

Introduction

Non communicable diseases (NCD) have emerged as the leading cause of morbidity and mortality in the world, killing more people than all other causes combined. NCDs encompass diseases like cardiovascular disease (CVD), cancers, diabetes, respiratory conditions like asthma and COPD and mental health disorders. 80% of NCDs occur inlow and middle- income countries. About 57 million deaths occurred globally in the year 2008, out of which 36 million

(almost two- third) were due to NCDs. [1] There isa sharp increase in the burden of NCDs in lower-income countries, where they imposehuge, avoidable costs. Among these NCDs, there has been an increase in the disease burden of CVD in recent years. In India, with a massive increase in population, there is expected to be a drastic increase in number of people 'susceptible' to CVD. One-fourth of the world inhabits the South-Asian countries and accounts for the highest proportion of burden of CVD compared to any other region globally. ([3] Data suggest that number of cases of CVD will increase from about 2.9 crore in 2000 to 6.4crore in 2015 (a 3.5 times increase in disease burden); the number of deaths as a resultof CVD will more than double in this period. [2] Deaths related to CVD occur 5-10 years earlier in South Asian countries as compared to the Western countries. [4] There has been a steady rise in prevalence of CVD in urban as well as rural India. In urban areas it has increased from 1% in the 1960s to 9% in the 1990s. In rural areas the rate has increased from 2% in the 1970s to 4% in the 1990s. [5] The NCMH (National Commission on Macroeconomics and Health) background papers state that although prevalence rates of rural population will remainlower than urban population, the prevalence rates will show an increasing trend, Higher prevalence in recent decades may reflect better clinical diagnosis, more health care facilities, a higher number of CHD patients in hospitals, greater survival, and aging of the population. [6])AMI in the South Asian population occurs in a younger population. The mean (SD) age for first AMI was lower in South Asian countries (53.0 [11.4] years) than in other countries (58.8 [12.2] years; P<0.001). [7] This can be explained by higher risk factor levels such as current and former smoking, alcohol consumption, hypertension, diabetes mellitus, a high waist to hip ratio, elevated ApoB100/ ApoA-I ratio and adverse psychosocial factors. AMI may result in several complications. The complications of AMI include ischemic, arrhythmic, mechanical, embolic and inflammatory outcomes. About 90%of patients with AMI develop some form of cardiac arrhythmia during or immediatelyafter the event. In 25% of the patients, these arrhythmias manifest within the first 24 hours. The risk of serious arrhythmias like ventricular fibrillation is greatest in the first hour and declines thereafter. ([8-10]) The incidence of arrhythmias is greater with an STEMI than with NSTEMI. Most peri-infarct arrhythmias are benign and self- limited. Only those which result in hypotension, increase in myocardial oxygen requirements or which predispose the patient to develop additional 'malignant' arrhythmias need monitoring and treatment.

Objectives

To determine the demography, presentation, patterns and treatments of cardiacarrhythmias, To assess the outcomes in these patients in hospital, at 1, and 6 months, and todetermine the predictors of mortality, To compare acute myocardial infarction (AMI) patients with and withoutarrhythmia as a complication and to estimate the determinants of arrhythmias.

Review of Literature

After a decline in the incidence of communicable diseases, presently, a rapid rise is seen in the incidence of non-communicable diseases. Narain et al state that in 2008, NCDs were the top killers in the South-East Asia region, causing 7.9 million deaths; the number of deaths is expected to increase by 21% over the next decade. One-third of the 7.9 million deaths (34%) occurred in those <60 years of age (compared to 23% in the rest of the world). At the dawn of the third millennium, the prevalence of non-communicable diseases is rising across the globe. It is predicted that, by 2020, non-communicable diseases will cause 70% of all deaths in developing countries. ([11] Among the non-communicable diseases, the major diseases are cardiovascular disease(ischemic heart disease [IHD] and strokes), diabetes mellitus, cancer and chronic pulmonary disease. The burden of these conditions affects countries worldwide but to

a greater extent in developing countries. Of the total deaths in the South-East Asia region (14.5 million), cardiovascular diseases accounted for 25%, chronic respiratory diseases 9.6%, cancer 7.8% and diabetes 2.1%. (4) Ischemic heart disease (IHD) occurs due to compromised blood supply to the myocardium. This is usually due to atherosclerotic narrowing of coronary vessels. Hypertension, dyslipidemia and diabetes and, lifestyle factors such as tobacco smoking, poor diet and lack of adequate physical exercise lead to IHD. IHD is the leading cause of mortality globally. The incidence of IHD is rapidly rising. About 8,00,000 people in the United States are affected by myocardial infarction (MI) and inspite of a better awareness of manifesting symptoms and better healthcare facilities, 2,50,000 patients die annually. [(12)] In a country like India [(13)], where health care access is not equitable, MI results in significant morbidity and mortality. Acute myocardial infarction (AMI) is one of the commonest diagnoses in hospitalized patients in developed countries. AMI comprises of-ST elevation myocardial infarction(STEMI) and non- ST elevation myocardial infarction (NSTEMI). The incidence of STEMI has declined in the U.S.A., from 121 per 100,000 population to 77 per 100,000 population. ($p < 0.05$). [(14)] It is the standard antiplatelet agent used in the treatment of STEMI patients. It permanently inactivates a key platelet enzyme, cyclo-oxygenase (COX). This leads to inhibition in the production of thromboxane- A_2, leading to inhibition of platelet aggregation. The enzyme can be regenerated back only after synthesis of new platelets. Aspirin has an established benefit in a variety of cardiovascular disorders including primary and secondary prevention of coronary heart disease, transient ischemic attack, and stroke, and in the acute therapy of patients with an ACS. The Antithrombotic Trialists' Collaboration reviewed the effect of antiplatelet therapy, mostly aspirin (in doses ranging from 75-1500 mg daily) in about 200,000 patients. [(15)] Antiplatelet therapy produced a 30 % reduction in the combined endpoint of subsequent nonfatal myocardial infarction (MI), nonfatal stroke, or vascular death patients with acute myocardial infarction. Secondary prevention plays an extremely important role in management of patients with AMI. The secondary prevention strategies can be classified into: Non- pharmacological: Smoking cessation, lifestyle modifications for control of weight, blood pressure, plasma cholesterol and sugar levels, Pharmacological: antiplatelet agents, anticoagulants, renin- angiotensin- aldosterone axis (RAAS) inhibitors, beta blockers, hypolipidemic agents, insulins and oral hypoglycaemic agents.

Material and methods

This is a prospective, follow-up, observational study with a total duration of 18 months. Patient recruitment was done in 14 months, All patients were followed- up at 1 month and 6 months from the date of recruitment, with a mean duration of follow-up of 4 months. The study was explained in detail to the patient, informed consent was obtained. The data were collected using a structured Case Record Form (CRF). We carried out the study in the Coronary Care Unit (CCU) and in-patient wards (common ward, semi- private and AC private blocks) of the Department of Cardiology. At Jay Prabha Medanta super Speciality Hospital, Patna, Bihar.

Inclusion criteria

Patients were recruited into either of the two groups:Group I: AMI only and Group II AMI with arrhythmia

Group I: patients with AMI only, fulfilling any two of the following three criteria:

ECG findings suggesting STEMI (ST segment elevation myocardialinfarction) or NSTEMI (Non-ST segment elevation myocardial infarction). Elevated cardiac markers (Creatinine phosphokinase, or troponin-T/I).

New onset chest pain or discomfort with a previous history of ischemicheart disease.

Group II: patients with AMI

Exclusion criteria
Patients treated elsewhere and referred to this hospital for further management without adequate and reliable information on prior treatments received, Patients in whom the 6-month follow up is not possible (eg. Patients from a faroff place, or with mental disorders).

The investigator visited the CCU everyday to screen all the patients and recruit those suffering from AMI. The admissions book as well as the case sheet for every patient was carefully scrutinised. An opinion was taken from cardiology residents regarding the diagnosis before recruitment of patients. Once a patient was identified for recruitment, he/ she was given an informed consent form (ICF), which explained in detail about the objective and the process of the study. All patients in the AMI with arrhythmia group were followed up at 1 and 6 months. The date of follow- up was ascertained based on their date of discharge. At 1 and 6 months, the patients were contacted and follow- up data were collected. We did a formal sample size calculation to determine the number of AMI patients required to be recruited into our study. Based on previous studies, we fixed the expected proportion of arrhythmias in AMI patients at 0.46. With a precision of 10% and confidence interval of 95%, our sample size of AMI patients was 95. The study was to be conducted in a limited period of time in the Coronary Care Unit (CCU) of Department of Cardiology, Jay Prabha Medanta super Speciality Hospital, Patna**.** From analysis of the records it was found that about 100 AMI patients developed arrhythmia in the year 2010. Hence we decided to recruit 100 patients in the AMI with arrhythmia group.

Results
A total of 202 patients presenting to Jay Prabha Medanta super Speciality Hospital, Patna**.** in 14 months with acute myocardial infarction (AMI), with or without arrhythmias were recruited into the study. Out of these 202 patients, 100 patients presented with AMI (STEMI or NSTEMI) only, and 102 patients who came with AMI either presented with or developed arrhythmia as a complication. Patients were recruited into the studyover a 14 months . All patients with AMI who developed arrhythmia were followed up after 1 month and 6 months. Out of the 102 patients, 95 (93.1%) patients completed follow- up at 1 month and 87 (85.3%) patients completed follow- up at 6 months.: The mean age of the patients was 64.6 (±13) years. Among the 102 patients, 71 (69.6%) were males and 31 (30.4%) were females. Most patients were from upper middle 48 (47.1%) and lower middle 33 (32.4%) social classes. The median distance from place of symptom onset to hospital was 8 (IQR 4.8-30) kilometres. Most of the patients resided in urban areas [85 (83.3%)]. It took the patients a median time of 12 (IQR 2.4-72) hours to reach the hospital from the time of onset of symptom. The mean duration of hospital stay was 9.1 (±5) days. 38 (37.3%) patients were current or former smokers and 27 (26.5%) patients consumed alcohol. Patients in the AMI only group were younger [56.7 (±13) years] than the patients in the AMI and arrhythmia group [64.6 (±13) years, $p< 0.001$]. There was comparable distribution of males and females in both the groups [68% males & 32% females vs. 69.6% & 30.4% females ($p = 0.805$) in AMI only and AMI with arrhythmia groups, More patients in the AMI only group came from lower middle [45 (45%) vs. 33 (32.4%)] and poor [27 (27%) vs. 15 (14.7%)] as compared to the AMI with arrhythmia group. Conversely, AMI with arrhythmia had more patients from rich[6 (5.9%) vs. 2 (2%)] and upper-middle [48 (47.1%) vs. 26 (26%), p,0.003] socio- economic strata. There were more patients who smoked [29 (29%) vs. 21 (20.6%), $p= 0.313$] and who consumed alcohol [23 (23%) vs. 16 (15.7%), $p= 0.375$] in the AMI group as compared to the AMI with arrhythmia group. Among the 102 patients in AMI with arrhythmia group, 7 (6.9%) patients had previous history

of stroke, 6 (5.9%) patients had atleast 1 previous episode of angina and 25 (24.5%) patients had a previous episode of myocardial infarction. More patients in the AMI with arrhythmia group had a history of myocardial infarction as compared to AMI only group. [25 (24.5%) vs 9 (9%), p< 0.003] Of the 92 patients who were administered drugs, 22 (21.6%) patients received amiodarone, a Class III anti- arrhythmic agent according to the Vaughan Williams classification. It was initially administered as a loading infusion over first 24 hours, followed by an oral maintenance dose. The loading infusion dose used was 1000mg/ 24 hours, given as 150 mg over first ten minutes, followed by 360 mg over the next six hours and 540 mg over remaining 18 hours. The oral maintenance doses ranged from 400 mg to 1600 mg/day. Amiodarone was used most commonly in patients with atrial [10 (9.8%)] and ventricular arrhythmias [12 (11.8%)]. Among the atrial arrhythmias, it was used in paroxysmal supraventricular arrhythmia [2 (2%) patients], atrial flutter [1 (1%) patients] and atrial fibrillation [7 (6.9%) patients]. Among the ventricular arrhythmias, it was used predominantly in ventricular tachycardia [6 (5.9%)] and ventricular fibrillation [4 (4%) patients]. The use of proton pump inhibitors declined in patients from 1 to 6 months [24 (26.7%) vs. 10 (12.3%), p = 0.001]. Among the 102 patients in the AMI with arrhythmia group, 18 (20%) and 15 (16.7%) patients used trimetazidine and nicorandil at 1 and 6 months respectively. The use of both of these drugs declined at 6months, with 5 [(6.2%), p = 0.001 for trimetazidine, p = 0.002 for nicorandil] patients using each of the drug. At the second follow up at 6 months, 5 patients were lost to follow up. Hence a total of 82 (80.4%) were followed- up. Among the 82 patients followed- up, 4 died, 3 had recurrent myocardial infarction and 1 had an episode of congestive cardiac failure. depicts the clinical outcomes of AMI patients with arrhythmias in hospital, from discharge to 1 month and from 1 month to 6 months) The multivariable logistic analysis showed that ejection fraction was a significant predictor for mortality [OR 0.86, 95% CI (0.78, 0.95), p = 0.003]. This means that as the ejection fraction increases, death is less likely to occur.

Discussion

There is little literature available from India which describes the patterns of peri- infarction cardiac arrhythmias and their management in the hospital. This study was performed in a unique population of patients those who developed cardiac arrhythmias after an episode of acute myocardial infarction (AMI). We assessed patient demographics, patterns of arrhythmias, the drug treatments and the rates of major outcomes at discharge, at one month and at six months. These patients were compared with patients presenting with AMI who did not develop cardiac arrhythmias. The mean age of patients was 64.6 (±13) years. This was comparable to the results obtained from previous trials and registry studies. (55;66) The HERO-2 trial describedbaseline characteristics of patients developing bundle branch block (BBB) in the post-infarction period. The median age of patients who developed LBBB was 67 (IQR 60– 75), those developing RBBB with inferior AMI was 62 (IQR 52–69.5). [(16)] The GUSTO-1 study (17) stated a higher incidence of sustained VT/VF with older age. The median age of patients in the VT only group was 64 (IQR 54-72) years, in VF only group was 62 (IQR 53- 71) years and in neither VT nor VF group was 61 (IQR 52- 70) years (p < 0.001). In our study more males (69.6%) than females (30.4%) developed arrhythmia after an attack of acute MI. The proportion of women developing arrhythmias in our study is lesser (30.4%) as compared to data from previous studies. In the HERO-2 trial, 48% of patients who developed new LBBB were women, among those who developed RBBB, 36% were women. Most of the patients (79.4%) were from the upper middle and lower middle socio- economic strata. Most of the patients (83.3%) came from an urban background. Among the 102 patients recruited, 37.3% were current or former smokers and 26.5% were current/ former alcoholics. These rates are lesser as compared to data documented in previous studies. It was shown in

previous studies that patients with conduction disturbances (bundle branch block, BBB) in the post- myocardial infarction period had more co- morbidities as compared to those without BBB. (55;66;68) In the present study, 59.8% patients had hypertension and 57.8% patients suffered from diabetes, 5.9% patients had a previous history of angina and 24.5% patients had atleast one previous episode of myocardial infarction. Rates in HERO-2 (16) trial ranged from 62-64% (for conduction abnormalities- LBBB and RBBB after AMI) for hypertension and 16%- 48% for diabetes. Robert J. Goldberg noted that those who developed ventricular fibrillation were more likely to be men and were less likely to have history of angina or hypertension as compared to those who did not develop VF during index hospitalization. (18) Previous studies have reported that pre-infarction angina may protect against out-of-hospital VF (OR 0.25, 95% CI 0.10 to 0.66, and OR 0.84, 95% CI 0.77 to 0.99 for two different studies, respectively). (70;71) This effect is presumably due to ischemic preconditioning. The GUSTO-1 study (17) reported that systemic hypertension and previous MI were associated witha higher risk of sustained VT and VF ($p < 0.001$). In the present study, 42.2% patients had congestive cardiac failure (CCF), of which 58.1% patients were placed in NYHA stage IV. Sinus bradycardia is defined as a heart rate of as less than 50 to 60 beats/min. In our study, 4 (4%) patients developed sinus bradycardia. Previous studies suggest an incidence of 15 to 25 percent of patients after acute MI. ([8)] The decreased incidence seen in our study could be due to two reasons. Firstly, the arrhythmias are known to occur in STEMI patients with an inferior wall infarct (these patients have increased Crimm A et al also pointed out that after admission to hospital the incidence of sinus tachycardia steadily declined as a result of normalization of the activated sympathetic system. ([19)] The arrhythmias documented in our study were observed after the patients were admitted to the hospital. This could be the reason fora lesser incidence of sinus tachycardia. At 6 months, among the 102 patients who were recruited into the study, 14 (13.7%) expired, 7 (6.9%) were lost to follow- up, 5 (4.9%) had recurrent MI, 4 (3.9%) had cardiac arrest, 3 (2.9%) developed CCF and 1 had an attack of stroke. . Goldberg et al reported lower ejection fraction for that patients who developed ventricular fibrillation as compared to patients who did not develop VF. ([19)] GUSTO-1 study stated that depressed ejection fraction was associated with a higher risk of sustained VT and VF ($P < 0.001$). ([17)] Bigger et al reported a 2.5 times (Hazard ratio 3.5, Chi square statistic 30.3, $p <0.001$)increase in risk of death in patients with LVEF <30% due to ventricular arrhythmias after myocardial infarction as compared to those with LVEF ≥ 30%. [(20)] There were certain limitations to this study. Patients who died soon after admission to the hospital could not be included into our study. Secondly, due to the small sample size of 102 patients (with AMI and arrhythmia), our study was underpowered to determine the effects of arrhythmia on outcomes with a greater degree of precision.

Conclusion

CVD is a major non-communicable disease in India with a high burden of morbidity and mortality. A large proportion of the cardiovascular diseases consist of coronary artery disease (CAD). Acute coronary syndrome (ACS), which encompasses acute myocardial infarction (AMI) [which includes ST- elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI)] and unstable angina (UA) is an important sub-class of CAD associated with significant mortality.

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