

The beneficial effect of famotidine in patients with acute myocardial infarction

Alhasan Mujtaba¹, Ibrahim A. Majeed², Mazin A. Hazzaa³, Saad A. Hussain⁴

¹College of Pharmacy, Al-Basrah University, Basrah;

²Department of Clinical Pharmacy, College of Pharmacy, University of Baghdad, Baghdad;

³Department of Medicine, College of Medicine, Al-Basrah University, Basrah;

⁴Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad, Baghdad; Iraq.

Abstract

Objective: Survivors of myocardial infarction (MI) are at increased risk of cardiac remodeling and heart failure. Activated neurohormones, including histamine, play a critical role in this regard. Data from experimental animals indicated that blocking the activity of histamine served as a rational choice in treatment of this disease. The study was designed to evaluate the effect of famotidine in management of patients with acute MI.

Method: The present study was a multicenter prospective randomized trial carried out at Al-Sader Teaching Hospital and Al-Fayhaa' General Hospital, Basra, Iraq during the period from August 2010 to August 2011. Sixty patients were allocated into two groups. Group 1 (31 patients) received famotidine (40 mg/day) and group 2 (29 patients) received placebo formula in addition to the currently used drugs. All patients underwent initial echocardiographic evaluation at admission and 30 days after randomization along with measurement of N-terminal pro-brain natriuretic peptide (Nt-proBNP) levels.

Results: Famotidine decreased the dilation of the left ventricle compared to placebo ($P < 0.05$), with an absolute decrease in left ventricular ejection fraction ($P < 0.05$). Famotidine treated patients also had a lower level of Nt-proBNP after completion of the study.

Conclusion: Famotidine appears to have a beneficial role in management of patients who survive myocardial infarction.

Key words:

Famotidine; Myocardial infarction; Nt-proBNP

Correspondence:

S.A. Hussain
Department of Pharmacology and
Toxicology, College of Pharmacy,
University of Baghdad,
Baghdad, Iraq.
saad_alzaidi@yahoo.com

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Introduction

Myocardial infarction (MI) is a major cause of morbidity and mortality worldwide [1]. Central to this disease is cardiac remodeling that occurs shortly after MI [2]. Various medications are used in survivors of MI with the sole purpose to limit the remodeling phase. Of these medications are β -blockers that act through interfering with the damaging effects of adrenaline and nor-adrenaline on the myocardium. Neurohormonal activation with adrenaline and nor-adrenaline occurs shortly after MI, and this is linked to the severity of remodeling after MI [3]. Some studies have reported that during myocardial ischemia and reperfusion, histamine is released from the heart of rats [4], dogs [5], guinea pigs [6], and humans [7]. Histamine is known to be one of the chemical mediators that have inotropic and chronotropic actions, in addition to vasoactive and arrhythmogenic properties [8]. Activation of histamine H-receptors results in slowing atrioventricular (AV) conduction; on the other hand, H₂-receptor stimulation causes sinus

tachycardia, AV node automaticity, and ventricular arrhythmias such as extrasystole and ventricular tachycardia [9]. Histaminergic signaling is also activated after MI and plays a detrimental role in cardiovascular diseases [10]. First, histamine, acting through the H₂-receptor, has a positive inotropic and chronotropic effects on the heart [10]. Arterial mast cells and their histamine content were implicated in the etiology of MI and in infarct regions as well [11]. Additionally, blockade of H₂-receptors may have a cardioprotective role during ischemic insults such as acute coronary syndrome [3]. It has been previously reported that famotidine, a histamine H₂-receptor blocker, protected the heart against ischemia-reperfusion injury in dogs [10] and also improved both symptoms of **congestive heart failure** and ventricular remodeling in the clinical setting [12]. The present study was designed to evaluate the effect of famotidine in ameliorating cardiac remodeling in patients who survived after acute MI attack.

Patients and methods

The present study was a multicenter prospective randomized trial carried out at Al-Sader Teaching Hospital and Al-Fayhaa' General Hospital, Basra, Iraq during the period from August 2010 to August 2011. More than 180 patients were evaluated and assigned as eligible for participating in this study; however, only 60 patients agreed and completed the study and thus are included. All patients were diagnosed as having ST-segment elevation myocardial infarction-acute coronary syndrome (STEMI-ACS). The diagnosis was made by the treating physician according to the ACC/ESC (The American College of Cardiology / European Society of Cardiology) criteria for definition of myocardial infarction Type 1.

Patients were included in the study if they have all of the following:

- 18 years age and above;
- have STEMI-ACS according to ACC/ESC definition of myocardial infarction;
- accept to participate in the study by signing informed consent;
- have no contraindication to all standard medications including anticoagulants, statins, aspirin, β -blockers and ACE inhibitors.

Patients were excluded from the study if they have either one of the following:

- unwilling to take the study medication or participating in the study program;
- need mandatory anti-ulcer medication for concomitant upper GIT disease;
- have end stage renal disease and needing dialysis, have neoplastic disorders or did received anti-neoplastic drugs previously;
- poor echocardiographic window preventing adequate measurements.

The study protocol was approved by the scientific committee in the College of Pharmacy, University of Baghdad and the Medical Ethics Committee in the Iraqi Ministry of Health. Those sixty patients were randomized into two groups: group 1, includes 31 patients treated with famotidine 40 mg/day (Medochemie, Limassol, Cyprus) on top of their usual currently followed treatment; group 2, includes 29 patients treated with placebo formula in addition to the currently followed treatment. Patients were selected if they survive to acute STEMI, and willing to comply with the study protocol.

Echocardiographic evaluation

All patients underwent an initial echocardiography (Vivid 3, GE Medical Systems, Milwaukee,

WI, USA) at presentation (median time from admission to evaluation was 2 days). Another echocardiography was also done 30 days after randomization. Assessment of left ventricle (LV) systolic function was done using the biplane method of disks (modified simpson's method) and LV volume was assessed using a single plane volumetric evaluation as recommended by guidelines [13].

Measurement of plasma Nt-proBNP levels

Five milliliter of venous blood was collected after a 30 minutes of rest from each patient at admission (all samples are collected in the first day of admission) and at the time of the second echocardiographic evaluation. Collected blood was then centrifuged and plasma separated and kept frozen at -40°C . Standard commercial kit (Biomedica, Vienna, Austria) based on a sandwich enzyme immunoassay was utilized for the determination of N-terminal pro-brain natriuretic peptide in the plasma [14].

Statistical analysis

All data are presented as mean \pm S.D. or plain numbers. Variables that are normally distributed are compared using *t*-test (for continuous variables) or chi-square test (for categorical variables); while variables that are not normally distributed are either converted to normal distribution using Log scale or are compared using Mann-Whitney U test; *P* values less than 0.05 were considered significant.

Results

Baseline clinical variables were similarly distributed between study groups, and no significant differences appeared between them as shown in Table 1 (*P* > 0.05).

Initially (at day 1), no significant differences were reported in plasma Nt-proBNP levels between the two groups before starting treatment randomization. After 30 days of treatment follow up, famotidine treated group had a significantly decreased levels of Nt-proBNP compared to placebo (*P* < 0.05)(Fig.1). This decrease in plasma levels of Nt-proBNP was associated with a reduction in the absolute increase in left ventricle end-diastolic volume (LVEDV)(Fig.2); moreover, there is other important finding, where famotidine-treated group also showed an absolute reduction in left ventricle ejection fraction (LVEF) compared to placebo, which already had an absolute increase in LVEF (Fig.3).

Table 1. Demographic data, clinical characteristics and echocardiography parameters of included patients.

Parameters	Famotidine group	Placebo group	P value
Number of patients	31	29	0.8 a
Sex (male)	19	18	0.87 a
Sex (female)	12	11	0.83 a
Residency (Rural)	19	18	0.87 a
Residency (Urban)	12	11	0.83 a
Age (year)	53.26 (9.43)	51.17 (9.0)	0.39 b
Weight (kg)	74.29 (10.61)	72.04 (9.4)	0.39 b
Height (m)	1.61 (0.07)	1.6 (0.08)	0.36 b
BMI (basal metabolic index)	28.45 (2.94)	28.27 (2.75)	0.8 c
Mycordial Infarction Type (anterior)	17	13	0.47 a
Mycordial Infarction Type (others)	14	16	0.72 a
Thrombolysis (positive)	13	11	0.68 a
Thrombolysis (negative)	18	18	1 a
Family history	26	26	1 a
Diabetes	12	9	0.51 a
Hypertension	23	24	0.88 a
CAD (coronary artery disease)	6	7	0.78 a
Smoking	20	16	0.5 a
Nt-proBNP	482.14 (1189.8)	192.78 (303.2)	0.33 b; 0.57 a
Serum Creatinine	93.61 (12.5)	98.91 (15.17)	0.14 b
High Sensitivity (hs)-CRP	8.43 (4.68)	6.68 (4.18)	0.13 b
Troponin	3.67 (2.62)	3.75 (2.37)	0.9 b
Creatine Kinase (CK)-MB	37.77 (15.31)	39.48 (13.66)	0.65 b
Left Ventricular End Systolic Volume	41.26 (9.71)	39.42 (9.74)	0.47 b
Left Ventricular End-diastolic Volume	80.86 (14.76)	78.41 (11.96)	0.49 b
Left Ventricular Ejection Fraction	0.48 (0.11)	0.5 (0.09)	0.61 b
Diastolic Dysfunction Class (normal)	4	4	1 a
Diastolic Dysfunction Class (REAR)	16	14	0.72 a
Diastolic Dysfunction Class (PNF)	6	9	0.44 a
Diastolic Dysfunction Class (RFP)	5	2	0.26 a

Data are presented as mean (S.D.) or plain numbers.

REAR, reduction of early filling velocity to atrial filling velocity (E/A) ratio; PNF, pseudonormal filling; RFP, restrictive filling pattern. a, chi-square; b, *t*-test, c: Mann-Whitney U test.

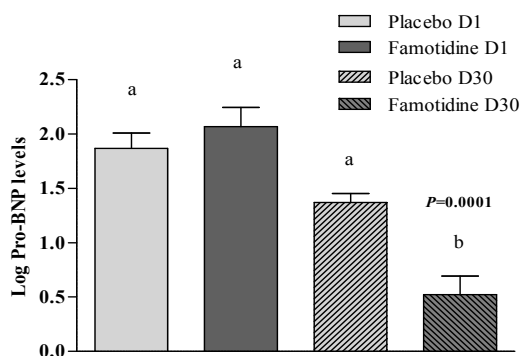


Figure 1. Effect of treatment with famotidine on the serum levels of the marker Nt-proBNP compared to placebo after 30 days in patients survived from acute MI. Values with different letters (a, b) represent significance ($P < 0.05$).

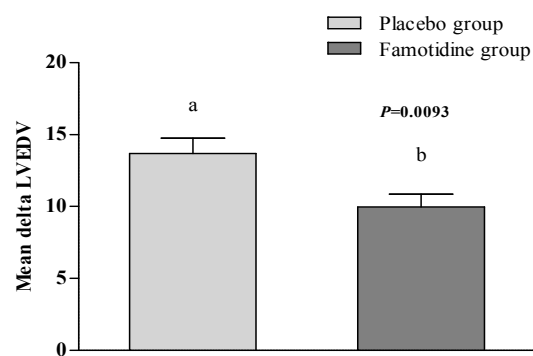


Figure 2. Effect of treatment with famotidine on left Ventricular end-diastolic volume (LVEDV) in patients survived from acute MI compared with placebo. Values with different letters (a, b) represent significance ($P < 0.05$).

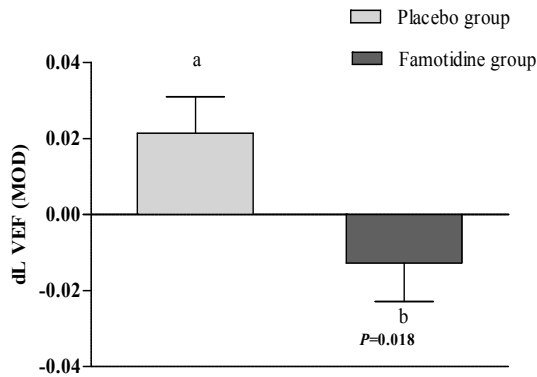


Figure 3. Effect of treatment with famotidine on left ventricular ejection fraction (LVEF) in patients survived from acute MI compared with placebo. Values with different letters (a, b) represent **significance** ($P < 0.05$).

Discussion

Current treatment of patients with MI aims to mitigate the effect of myonecrosis on LV remodeling [15]. Such treatments include timely reperfusion, β -blockers, ACE inhibitors and aldosterone antagonists [16]. The rationale of these medications is to limit the adverse effects of activated neurohormones induced by ischemia and MI [16]. In particular, β -blockers act through blocking the β_1 receptor; these β receptors are linked to Gs proteins and upon activation they lead to an increase in cAMP concentration [17]. This increase in cAMP concentration is linked to the adverse effect of sympathetic overactivation in cardiovascular disease [18, 19].

Interestingly, histamine is also reported to be elevated during ischemia and after MI, this activity is related to adverse outcomes [20, 21]. Meanwhile, this activity is mediated through the activation of H2 receptors [4]. H2-receptor is linked to Gs proteins just like β -blockers and upon activation they also lead to an increase in cAMP concentration [22]. Although histamine H2-receptors are expected to be blocked by H2-antagonists, famotidine is about 20 to 50 times more potent than cimetidine and 6 to 10 times more potent than ranitidine in this respect [23]. Moreover, the hemodynamic effects of famotidine is more prominent than both cimetidine and ranitidine [24]; this can explain the rationale behind using famotidine in the present work. Indeed famotidine was shown to decrease the activity of both Gs and cAMP concentrations in a variety of tissues including the heart [22]. Accordingly, the rationale of blocking the histamine over-activation after MI with the most potent H2-receptor blocker,

famotidine, is clarified [25]. Several trials have shown the benefit of famotidine on cardiovascular disease [10, 12, 26, 27]. First of all, animal studies documented that famotidine may have cardio-protective effect in ischemia-reperfusion injury with consequent reduction in infarct size [10]. Other studies reported that famotidine improves echocardiographically measured LVEF and LVEDV (a measure of LV remodeling) and infarct size [28].

Human studies started with a retrospective evaluation of patients taking famotidine compared to other treatments and found that patients with heart failure taking famotidine had a lower heart failure score (New York Heart Association, NYHA class), Nt-proBNP, and even mortality [26]. These results were also documented by prospective randomized trial in patients with stable heart failure [12]. According to updated literature evaluation, there are no studies on patients who survived myocardial infarction. The effect of famotidine on estimation of LVEF was conflicting between studies; while animal studies showed an improvement in LVEF, human studies in patients with stable heart failure and severe LV systolic dysfunction showed no benefit from famotidine. The present study documented that famotidine may lead to an absolute decrease in LVEF compared to placebo. This difference may be partly attributed to the difference in measures implemented during estimation of LVEF. Both human and animal studies used linear measures of LVEF which is confined to a single plane and may not adequately reflect the regional wall abnormalities (common after MI)[28]. We measured LVEF by the volumetric biplane method of disks (modified Simpson's method) which is accurately correlated with LV volumes and LVEF especially after MI and it is the method of choice according to the guidelines [13]. There is no wealth of data on the effect of famotidine on Nt-proBNP; however, since Nt-proBNP is released from the heart in relation to stretching and its serum levels correlated with heart failure status, the observed benefit of famotidine on LVEDV should be translated to a reduction in Left ventricular end-diastolic pressure (LVEDP), and hence stretching on the heart [29]. This is also true for patients with stable heart failure as Kim *et al* demonstrated that famotidine reduces LV remodeling as well as BNP levels after 20 weeks of follow up [12].

Although the present study has revealed an important issue regarding the rationale for using famotidine during treatment of patients with MI, the power of the study is compromised by the small number of patients enrolled in the study; the single-

blind approach followed may also predispose to researcher's bias which may influence the study outcome. The prognostic power of the benefit of famotidine in patients with MI is not yet known; however, it has a positive effect on Nt-proBNP which is well correlated with prognosis [30, 31]; so it should be anticipated that famotidine may have a positive effect on mortality and morbidity in patients surviving MI. In conclusion, adding famotidine on top of the currently used treatments of myocardial

infarction may be of benefit in terms of reduction in remodeling and heart failure score.

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