Anxiolytic Medication Use Does Not Have a Protective Effect Against Complications After Acute Myocardial Infraction

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Abstract: Anxiety is very common after acute myocardial infarction (AMI) and has been associated with higher complication rates and longer length of stay (LOS). The protective effect of anxiolytics against these complications is conflicting. The purpose of this study was to check the effect of anxiolytic medications use on complication rates after AMI. Sociodemograhpics, clinical variables, use of anxiolytic and beta blocker medications were extracted from medical records after patients have been discharged. A total of 200 participants were included in the study. Only 15% of the sample received anxiolytic medication and 23.5% developed complications. The use of anxiolytic medication did not decrease or independently predict in-hospital complication. Moreover, they did not decrease the LOS. Being smoker or has a previous AMI were independent predictors of in-hospital complications. In conclusion, the use of anxiolytic medication does not have any protective effect against the complications.
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1. Introduction

Anxiety is considered one of the earliest psychological responses to acute coronary syndrome events including acute myocardial infraction (AMI) (Moser et al. 2003). Anxiety has high prevalence rates after AMI and has been associated with higher rates of complications and mortality (Frasure-Smith et al. 2008; Moser et al. 2007). The prevalence of anxiety early after AMI is approximately 70% to 80% (Abed et al. 2013; Frasure-Smith 1991; Frasure-Smith & Lesperance 2008; Frasure-Smith et al. 1995). Previous studies showed that as many as 26% of patients with AMI had anxiety levels higher than patients with psychiatric disorders (Moser et al. 2003).

Patients who are anxious after AMI have approximately 6 times higher risk for ventricular complications or recurrent ischemia than patients who are non-anxious (Moser et al. 2003; Watkins et al. 2002). They are also at two times higher risk for atrial complications (Moser et al. 2003; Watkins et al. 2002).

Anxiety has been shown to significantly impact recovery after AMI (Crowe et al. 1996). Patients with high anxiety during the first 48 hours after AMI have 4.9 times risk of developing in-hospital complications such as reinfarction, recurrent ischemia, ventricular fibrillation, or tachycardia.(Moser et al. 2003). Anxiety is related to increased length of hospital stay, and severity of chest pain early after AMI (Bengtson et al. 1996; Costa et al. 1985; Crowe et al. 1996; Davies et al. 1993; Ketterer et al. 2000). Patients who are anxious while hospitalized also have higher long-term complication rates including a higher rate of recurrent myocardial infarction, unstable angina (Frasure-Smith et al. 1995; Grace et al. 2004) and a 3-fold increase in five year mortality (Frasure-Smith 1991).

The relationship between anxiety and complications has been conceptualized to work through sympathetic nervous system (SNS) arousal (Moser et al. 2003). Activation of the SNS triggers a cascade of physiological responses that increase myocardial oxygen consumption (Kamarck et al. 1991; Muller et al. 1989), enhance cardiac vascular reactivity (Panza et al. 1991), platelet aggregation (Brezinski et al. 1988), and lower the dysrhythmic threshold (Abu Ruz et al. 2011; Kamarck & Jennings 1991; Muller et al. 1989). Moreover, anxiety is associated with hypercoagulation (von Kanel et al. 2006), hyperlipidaemia (Vural et al. 2007), immune suppression (Pitsavos et al. 2006), and reduced heart rate variability (Miu et al. 2009). From behavioral point of view, anxiety might negatively affect adherence to specific diet, physical activity and smoking cessation (Bonnet et al. 2005; Kuhl et al. 2009).

Patients might have different levels of anxiety. These levels depend on: Patient's perception of the area where the patient is waiting or going to be admitted (usually Emergency Room (ER) and Intensive Care Unit ICU), perceived control level, fear of death, family support, and previous experience (Abed et al. 2013; Abu Ruz et al. 2011). Anxiolytics should be given to AMI patients as early as possible because this is the time when the anxiety levels will be

the highest (Abed et al. 2013; An et al. 2004). Unfortunately, critical pathways for AMI management do not incorporate specific strategies for anxiety management (Corbelli et al. 2003; Fonarow 2003).

Complications of AMI resulting from high anxiety levels in ER and ICU will increase the length of stay, contributing to the enormous increase in the cost of treatment and reduce the likelihood of survival. Despite the importance of reducing anxiety for recovery, anxiety is not routinely assessed nor effectively managed in the clinical setting after AMI (Abed et al. 2013).

2. Material and Methods

General Objective: The major goal of this study was to check the effect of anxiolytic medications use on complication rates after AMI.

Research Hypotheses:

1. Patients who received anxiolytic medication will have lower complications rate than those who did not receive these medications.
2. Patients who received anxiolytic medication will have shorter length of stay than those who did not receive these medications.
3. Use of anxiolytic medication will have a protective effect against complication after controlling demographic (i.e. age and gender) and clinical factors (i.e. history of hypertension and diabetes mellitus, previous AMI, and use of beta blockers)

Research design, sample and setting: A descriptive design was used in this study. The study was conducted at a major private specialized cardiac center in Amman, Jordan. The inclusion criteria of the sample were: 1) a diagnosis of AMI evidenced by elevated cardiac enzymes and electrocardiogram changes, 2) 18 years old and above, and 3) no previous psychiatric disorder. Two hundred patients were included in this study

Ethical Considerations: After the ethical committee in the center read the proposal and gave the approval, a letter confirming that was sent to the Principle Investigator by the medical director accepting doing the study at the center

Data collection: Research assistants started data collection by reviewing medical records after the participants were discharged from the hospital. Inter-rater reliability among the research assistant was 96%. All of them asked to extract data from 5 files and the Principle Investigator checked them for consistency.

Demographic and clinical variables: Demographic and clinical variables included age, gender, marital status, history of hypertension, angina, diabetes mellitus, previous AMI, ejection fraction, Killip class on admission, and use of beta blocker were extracted from medical record

Anxiolytic medication use: Medical records were reviewed to determine whether anxiolytic medication was administered to patients in the ER and ICU. The use of anxiolytic medication in each setting was scored either 0 to indicate 'no use', or 1 to indicate 'use'.

In-Hospital Complications. Criteria from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) study were used to define in-hospital complications (Investigators 1993). In-hospital complications were defined as the presence of any of the following: (1) acute recurrent ischemia evidenced by new onset of chest pain, electrocardiographic changes, or hemodynamic instability; (2) reinfarction evidenced by recurrent positive creatine kinase–MB; (3) sustained ventricular tachycardia (>15 seconds), or any ventricular tachycardia requiring pharmacological and/or electrical intervention due to hemodynamic instability or chest pain; (4) ventricular fibrillation; or (5) in-hospital death.

Length of stay: Medical records were reviewed to determine the length of stay in the ICU and in the hospital. The length of stay was measured in days.

Data Analysis: SPSS software version 20.0 was used to analyze the data (SPSS Inc., Chicago, IL, USA). Descriptive statistics with numbers and frequencies was used for the purposes of this study. To test if the use of the anxiolytics decreased the number of complications and the length of stay in the hospital (hypothesis 1 and 2) Independent sample t-tests was used. Hierarchical logistic regression was used to evaluate the ability of anxiolytic medication use to predict the probability of in-hospital complications, (Hypothesis 3). In the first block, age and gender were entered. In the second block; history of diabetes mellitus, hypertension, myocardial infarction, beta blocker use and smoking history were entered. In the final block, the use of anxiolytic medication was entered. Alpha was set at 0.05 for all analyses. The results of the logistic regressions are reported as odds ratios with 95% confidence intervals.

3. Results

Two hundred patients were included in the study. Demographic and clinical characteristics of the sample are described in Table 1. There was no significant difference between the two groups in any of the sociodemograhpics or clinical characteristics

The mean age for the participants was 66.8 ± 11.8 years. Most of the participants were male (70.5%) with a history of hypertension (73%). Fifteen percent only used anxiolytics during hospitalization. Approximately quarter of the sample developed complication. Majority of the patients has previous angina and more than have of them did CABG surgery. The use of anxiolytics did not make any difference

regarding the length of stay in ICU/hospital (mean [SD], 4.72 [7.66] vs 5.84 [6.42], P = .49) or in the mean number of complications (mean [SD], 0.48 [1.17] vs 0.60 [1.07], P = .58).

Table 1: Sociodemograhpic and clinical characteristics of the sample

Variable	Total sample (n=200)	Received anxiolytics (n=30)	Did not receive anxiolytics (n = 170)
Gender			
Male	141 (70.5)	22 (73.3)	119 (70)
Female	59 (29.5)	8 (26.7)	51 (30)
Age	66.8 ± 11.8	67.4 ± 12.8	66.7 ± 10.9
History of hypertension	146 (73.0)	19 (63.3)	127 (74.7)
History of diabetes	76 (38.0)	8 (26.7)	68 (40.0)
History of previous AMI	125 (62.5)	17 (56.7)	108 (63.5)
History of previous angina	171 (85.5)	25 (83.3)	146 (85.9)
History of previous CABG	115 (57.5)	14 (46.7)	101 (50.5)
History of stent use	90 (45)	15 (50)	75 (44.1)
Has any complication during hospitalization	47 (23.5)	10 (33.3)	37 (21.8)
Smoking			
Never smoked	60 (30)	5 (16.7)	55 (32.4)
Current smoker	53 (26.5)	8 (26.7)	45 (26.5)
Former smoker	87 (43.5)	17 (56.6)	70 (41.1)

Values are given as frequency (%) or mean ± SD.
CABG: Coronary artery bypass graft surgery

Among all the variables that were used in the logistic regression, only history of previous AMI and being a smoker were the independent predictors of in-hospital complications. Patients with previous AMI were at 2.44 times higher risk for developing complication than those with no previous AMI history. Moreover, being smoker increased the risk for developing complication by 118%. Anxiolytic use was not an independent predictor of complication after AMI (table 2).

Table 2: Independent predictors of in-hospital complications

Predictor	OR	95% confidence interval	B	Wald	P- value
Age	1.01	0.98-1.04	0.01	0.02	0.90
Gender	1.88	0.88-4.02	0.63	2.61	0.11
Previous AMI	2.44	1.06-5.57	0.89	4.43	***0.04****
Diabetes	1.95	0.93-4.10	0.67	3.11	0.07
Hypertension	0.42	0.16-1.16	-0.86	2.80	0.09
Use of beta blocker	1.40	0.58-3.37	0.34	0.56	0.46
Smoking	2.18	1.18-3.99	0.79	5.91	***0.03****
Anxiolytics	1.76	0.69-4.49	0.57	1.41	0.24

4. Discussions

To our knowledge, this was the first study that checked the effects of anxiolytics on in-hospital complications after AMI in Jordan. The results of our study suggest that administration of anxiolytics did not eliminate the effect of anxiety on in-hospital complications or on hospital LOS. Moreover, the use of anxiolytic medication was not an independent predictor of complication after AMI. This conclusion is supported by results of a similar study (Abed et al. 2013) in which patients received anxiolytics during hospitalization for AMI. Mona et al showed that the use of anxiolytics was not associated with anxiety level and did not reduce the probability of in-hospital complications. We demonstrated in a previous study (Abu Ruz et al. 2011) that history of previous AMI and smoking are independent predictors of in-hospital complications. The results of this study supports these findings.

It was hypothesized that early administration of anxiolytics after AMI would eliminate the relationship between anxiety, complications and LOS. This hypothesis was based on the theory that anxiety stimulates the SNS (Fricchione et al. 1986; Kamarck & Jennings 1991; Niaura et al. 1992) will result in a series of physiological responses including enhanced coronary vascular tone (Panza et al. 1991) platelet aggregation (Brezinski et al. 1988) increased myocardial oxygen consumption, and lowered threshold for dysrythmias (Kamarck & Jennings 1991; Muller et al. 1989). Combined, these responses would increase patients' vulnerability to ischemic and dysrhythmic complications, which usually occur in the first 48 to 72 hours after AMI. During this period, the administration of anxiolytics should limit the stimulatory effects of anxiety on the SNS and subsequent complications.

Contrary to the previous theory our findings suggest that anxiolytic medications were under

prescribed and did not have a protective effect on in-hospital complications. This might be due to different factors. These factors might include but not limited to: the duration of anxiolytics use, route and dose of administration, type of anxiolytic medication and severity of illness. Moreover, two important causes are: a) In the early phase of AMI, the health care team primary concern will be the hemodynamic stability, and b) there is no recommend guidelines on how and when anxiolytic medication should be incorporated into the management of acutely ill patients including patients with AMI.

In a study checking the effect of routine administration of oral diazepam (10 mg) for two days in patients after AMI, (Dixon et al. 1980) found no significant differences in dysrhythmia incidence. In contrast, in a randomised clinical trial (Melsom et al. 1976) examined the effect of a 10 mg intravenous loading dose of valium followed by three days of oral (15 mg) daily in patients after AMI. These investigators found a significant reduction in urinary catecholamines, which suggested a cardioprotective effect of an anxiolytic medication.

Comparable to previous studies (De Jong et al. 2004; Jacob et al. 2003) results which demonstrated that anxiolytic medications were under-prescribed and underused in clinical settings, we found that only 15% of our patients received anxiolytic medication. De Jong et al. (2004) found that only 30% of patients after AMI (N = 912) recruited from Australia, England, Japan, South Korea and the United States received anxiolytic medication in the ICU, even though more than half of these patients reported high anxiety levels.

5. Conclusion and recommendations

Use of anxiolytics in patients with AMI did not reduce the probability of in-hospital complications. Anxiolytic medications were not routinely used or incorporated in the management guidelines. Clinical guidelines for the management of patients with an AMI should integrate appropriate use of anxiolytic medication to improve patients' outcomes.

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