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Efficacy and Safety of Lorazepam Relative to Chest Pain, Delirium, Arrhythmias, and Sleep Satisfaction in Patients with Acute Coronary Syndrome: A Randomized, Double-Blind, Placebo-Controlled Study

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Abstract

Background: Patients with anxiety commonly occurs after an Acute Coronary Syndrome (ACS). The standard treatment to relieve anxiety is the sedation drugs. Lorazepam can effectively relieve the symptoms and *affect* the symptoms confusion and mood changes.

Objective and methods: To investigate the efficacy and safety of lorazepam relative to chest pain, delirium, arrhythmias, and sleep satisfaction compared to placebo in patients with acute coronary syndrome. This prospective, randomized, double-blind clinical trial included ACS patients who were treated during the April 2016 to June 2018 study period. The study population was randomized into the lorazepam group or the placebo group. Subjects received either lorazepam 0.5 mg oral QD or placebo, which was administered for at least 7 days from the first day until discharge or transfer.

Results: A total of randomized controlled trials included 248 patients. The placebo seems to be non-inferior to lorazepam for the events (chest pain, delirium and arrhythmias) (P value=0.001). The primary endpoint occurred at a higher rate in the lorazepam group than in the placebo group.

Conclusion: Placebo was found to be non-inferior to lorazepam for the cardiac events evaluated in this study-chest pain, delirium, and arrhythmias. The mean score of first-night sleep satisfaction was significantly higher in the lorazepam group than in the placebo group, which suggests the efficacy of lorazepam in ACS patients to relieve anxiety and improve the quality of sleep during the first night of their hospital stay.

Keywords: Acute coronary syndrome; Chest pain; Delirium; Lorazepam

Introduction

Acute coronary syndrome continues to be a significant cause of morbidity and mortality worldwide. Rapid reperfusion via primary Percutaneous Coronary Intervention (PCI) is the standard goal of treatment. Combined with appropriate medical management, PCI can improve short- and long-term outcomes following Myocardial Infarction (MI). If PCI cannot be performed rapidly, patients with ST-Elevation Myocardial Infarction (STEMI) can be treated with fibrinolytic therapy. PCI has been widely used to treat obstructive Coronary Artery Diseases (CADs), including unstable angina, recurrent angina after Coronary Artery Bypass Grafting (CABG), and Acute Myocardial Infarction (AMI), with a resulting reduction in clinical symptoms and mortality rate [1]. Anxiety commonly develops after an AMI [2-4]. Anxiety, increased heart rate, and augmented contractility with significantly increased myocardial workload and myocardial oxygen consumption are common after-effects in patients who have experienced a myocardial ischemic event [5,6]. Pain relief is very important in this patient population not only for improving patient comfort, but also because pain is associated with sympathetic activation, which causes vasoconstriction, increases the workload of the heart, and reduces myocardial oxygen demand. Titrated Intravenous (IV) opioids (e.g., morphine) and benzodiazepines (e.g., lorazepam) are the analgesics most commonly used in this context. However, morphine use is associated with slower uptake, delayed onset of action, and diminished effects of oral antiplatelet agents that may lead to early treatment failure in susceptible individuals [2]. Moreover, morphine can cause hypotension and respiratory failure.

Therefore, the standard treatment for relieving anxiety is sedation drugs. Lorazepam is routinely prescribed in all MI patients every night until discharge. Lorazepam can effectively relieve the symptoms of anxiety or anxiety associated with depressive symptoms and insomnia. Insomnia and/or restlessness may effectuate symptoms that include tachycardia, rapid breathing or shortness of breath, restlessness, confusion, and mood changes. The dose of lorazepam most commonly prescribed to ACS patients is 0.5 mg oral QD in the evening before bed. A previous study reported that more chest pain, arrhythmias, and mortality were observed in AMI patients with higher levels of anxiety than in those with lower levels of anxiety (19.6% *vs.* 6%, p=0.001) [6].

To our knowledge, there has been no well-designed, randomized, prospective clinical trial that compared treatment strategies in patients with ACS. Few studies have assessed the efficacy and safety of lorazepam in ACS patients. Accordingly, the aim of this randomized controlled trial was to investigate the efficacy and safety of lorazepam relative to chest pain, delirium, arrhythmias, and sleep satisfaction compared to placebo in patients with ACS.

Patients and Methods

Patient population

This prospective, randomized, double-blind clinical trial included ACS patients who were treated at the Cardiac Care Unit or the Intermediate Cardiac Care Unit of the Division of Cardiology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during the April 2016 to June 2018 study period. Patients aged older than 18 years with good consciousness and hemodynamic stability were eligible for inclusion. Patients with one or more of the following were excluded: 1) suspected infection, such as sepsis, urinary tract infection, or pneumonia; 2) history of psychiatric problems; 3) sedative drug use within 1 month prior to randomization; 4) contraindications for lorazepam, such as liver failure and allergy; and/or 5) history of alcohol addiction. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) (COA no.752/2558), and all patients provided written informed consent to participate.

Study protocol

Patients were randomly assigned to receive 0.5 mg lorazepam or placebo once daily using the double-dummy technique to ensure blinding of both the patient and the nurse dispensing the medication. Randomization codes were generated by the pharmacy at our centre using a computer-generated random number scheme based on individual assignment. Lorazepam and placebo were packaged according to study group assignment. Lorazepam and placebo were packaged in a capsule having the same volume, size, and color. The medication packets were stored at the pharmacy, and the study group assignments were known only to involved pharmacy staff until after the study was completed.

Measurements

The primary endpoint was the first occurrence of chest pain, delirium, or arrhythmias. The secondary endpoint was sleep satisfaction. Treatment (PCI or no-PCI) and disease (STEMI or non-STEMI) subgroup analysis was also performed between groups for each of the primary endpoint diagnoses (chest pain, delirium, and arrhythmias). Before *lorazepam* was *administered*, patients were assessed for the presence of delirium. Subjects received either lorazepam or placebo 0.5 mg oral QD in the evening for at least 7 days from the first day until discharge or transfer. All patients had continuous bedside ECG telemetric monitoring.

Chest pain assessment: Assessment of chest pain involved documentation of pain *location*, *frequency*, *duration*, severity, and pattern. Pain is subjective so the use of pain scores, visual analogues, and pain scales are helpful for quantifying the severity of chest pain and the effectiveness of the treatment administered [7,8]. Accordingly, a Numeric Rating Scale (NRS) for pain was used to assess the severity of chest pain, with a 0 indicating no pain, a 5 indicating moderate pain, and a 10 indicating the worst possible pain.

Delirium assessment: All study patients were assessed for the presence of delirium every 8 hours (at 0600, 1400, and 2200) using the Thai Delirium Rating Scale [9].

Cardiac arrhythmia assessment: The occurrence, frequency, and duration of cardiac arrhythmia, defined as premature ventricular tachycardia, atrial fibrillation, heart block, ventricular fibrillation, or ventricular tachycardia, was recorded from telemetry.

Satisfaction of sleep: Sleep satisfaction was assessed using 5 questions that were self-rated by the patient using a 6-point Likert scale, with a 0 indicating full disagreement, and a 5 indicating full agreement. All questions related to the patient's level of sleep satisfaction after waking up in the morning.

Statistical analysis

Descriptive statistics were used to summarize demographic and clinical data. Qualitative data were compared using chi square test or Fisher's exact test, and are expressed as number and percentage. Quantitative data were compared using Mann-Whitney U test, and are presented as mean ± standard deviation. Z-test for non-inferiority was employed to test for non-inferiority between the study drug and placebo. Comparison of primary endpoint data between groups is shown as percentage difference between groups and 95% confidence interval. SPSS Statistics (version xx; SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses, and a p-value of less than 0.05 was regarded as being statistically significant for all tests (Figure 1).

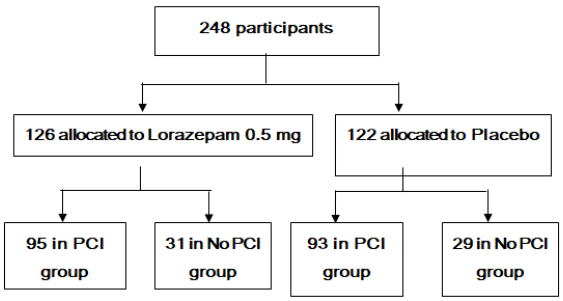

Figure 1: Exploratory analysis flowchart. Patient eligibility, group for analysis selection, PCI: Percutaneous Coronary Intervention.

Results

Two hundred and forty-eight patients were included. The study consisted of 248 patients, 126 cases in the lorazepam group and 122 cases in the placebo group. The baseline demographic and ejection fraction was higher in the placebo group as compared to the lorazepam group (51.9+10.5 *vs.* 49.3+10.1, p=0.044) (Table 1). Baseline LDL level in the case group is slightly higher when compared to the control group, (125.7+33 *vs.* 93.7+34, p=0.06). Other baseline laboratory data is similar between the two groups (Table 2). The effects of the study of medications on chest pain, delirium and arrhythmias are shown in Table 3. The placebo seems to be non-inferior to lorazepam for the events (chest pain, delirium and arrhythmias) because the P

value=0.001 when to use Z-test for non-inferiority with 10% margin of non-inferiority.

Characteristics	Lorazepam n=126	Placebo n=122	P value
PCI			0.878
Yes	95 (75.4)	93 (76.2)	
No	31 (24.6)	29 (23.8)	
Sex			0.39
Male	90 (71.4)	93 (76.2)	
Female	36 (28.6)	29 (23.8)	
Age (mean+SD)	62.4+11.2	61.0+12.1	0.365
Weight (mean+SD)	64.7+12.6	66.9+14.0	0.193
Height (mean+SD)	167.7+9.4	164.3+9.1	0.194
Systolic blood pressure (mean +SD)	129.4+21.8	126.0+19.2	0.194
Diastolic blood pressure (mean +SD)	76.7+13.8	74.9+13.8	0.215
Heart rate (mean+SD)	82.4+15.0	81.7+15.4	0.704
ECG rhythm (initial)			0.074
NSR	119 (94.4)	116 (95.1)	
Atrial fibrillation	1 (0.8)	4 (3.3)	
Heart block	6 (4.8)	2 (1.6)	
Clinical diagnosis, n (%)			0.669
STEMI	96 (76.2)	95 (77.9)	
Non STEMI	30 (23.8)	27 (22.1)	
Underlying Disease, n (%)			
Diabetes mellitus	36 (28.6)	40 (32.8)	0.472
Hypertension	62 (49.2)	69 (56.6)	0.246
Dyslipidemia	38 (30.2)	51 (41.8)	0.056
Smoking	43 (34.1)	40 (32.8)	0.823
Kidney disease	5 (4.0)	4 (3.3)	0.772
Family history	12 (9.5)	5 (4.1)	0.091
Killip class			
Class I-II			
Class III-IV			
Ejection fraction (mean+SD)	49.3+10.1	51.9+10.5	0.044

Table 1: Patient demographics and baseline characteristics (n=248). PCI: Percutaneous Coronary Intervention; NSR: Normal Sinus Rhythm; STEMI: ST Elevation Myocardial Infarction.

Laboratory	Lorazepam n=126	Placebo n=122	P value
BUN	16.3+8.6	18.4+10.2	0.213
Creatinine	1.2+1.1	1.2+0.9	0.89
CBC			
Hematocrit	39.5+6.0	40.7+6.3	0.097
Hemoglobin	12.9+2.1	13.4+2.2	0.077
WBC	12723.4+13971.7	13065.2+11223.5	0.833
Platelet	253352 +77768.2	253445+90971.2	0.993
Electrolyte			
Sodium	138.4+3.7	138.1+3.6	0.467
Potassium	3.9+0.4	3.8+0.4	0.141
Chloride	99.3+10.6	99.7+4.7	0.706
Bicarbonate	22.4+3.5	22.1++2.6	0.495
ALT	136.7+138.1	129.2+193.2	0.84
AST	105.4+133.5	148.1+119.2	0.544
PT	12.4+2.9	13.7+4.8	0.217
PTT	27.0+5.9	31.0+19.3	0.304

Table 2: Laboratory results at baseline between two groups. CBC: Complete Blood Count; WBC: White Blood Cell; ALT: Alanine Aminotransferase (SGPT); AST: Aspartate Aminotransferase (SGOT); PT: Prothrombin Time; PTT: Partial Thromboplastin Time.

Event	Lorazepam n=126	Placebo n=122	95%CI for difference	P value
Chest pain	8 (6.3)	7(5.7)	0.6% (-4.7% to 5.8%)	0.001
Delirium	5 (4.0)	2 (1.6)	2.4% (-1.5% to 6.5%)	<0.001
Arrhythmias	18 (14.3)	14 (11.5)	2.8% (-4.3% to 9.9%)	0.001

Table 3: Incidence of chest pain, delirium and arrhythmias, P value for Z-test for non-inferiority with 10% margin of non-inferiority.

The primary endpoint occurred at a higher rate in the lorazepam group than in the placebo group (Table 4). The differences between the drugs were not significant. In PCI group, event rate occurred at a lower rate in the lorazepam group than in the placebo group whereas in no PCI group, event rate occurred with higher rate in the lorazepam group than in the placebo group (Table 5).

The efficacy of lorazepam in both groups in STEMI seemed to be similar but in the chest pain in lorazepam group is less than one (Table 6). There were significant differences in satisfaction of sleep by those living with others.

	PCI			No PCI		
Event	**Lorazepam n=95**	**Placebo n=93**	**P value**	**Lorazepam n=31**	**Placebo n=29**	**P value**
Chest pain	3 (3.2)	4 (4.3)	0.719	5 (16.1)	3 (10.3)	0.708
Delirium	1 (1.1)	1 (1.1)	0.988	4 (12.9)	1 (3.4)	0.355
Arrhythmias	10 (10.5)	9 (9.7)	0.847	8 (25.8)	5 (17.2)	0.421

Table 4: Incidence of chest pain, delirium and arrhythmias by treatment subgroup, PCI: Percutaneous Coronary Intervention; STEMI: ST Elevation Myocardial Infarction.

	STEMI			Non STEMI		
Event	**Lorazepam n=96**	**Placebo n=95**	**P value**	**Lorazepam n=30**	**Placebo n=27**	**P value**
Chest pain	1 (1.0)	4 (4.2)	0.211	7 (23.3)	3 (11.1)	0.304
Delirium	1 (1.0)	1 (1.0)	0.749	4 (13.3)	1 (3.7)	0.356
Arrhythmias	11 (11.5)	11 (1.5)	0.579	7 (23.3)	3 (11.1)	0.304

Table 5: Incidence of chest pain, delirium and arrhythmias by disease subgroup, STEMI: ST Elevation Myocardial Infarction.

Satisfaction of sleep	Lorazepam n=126	Placebo n=122	P value
Day 1	4.39	3.92	<0.05
Day 2	4.16	4.01	0.16
Day 3	4.28	4.12	0.93

Table 6: Satisfaction of sleep after wake up in the morning between two groups.

Discussion

The present study compared the effects of lorazepam and placebo relative to chest pain, delirium, arrhythmias, and sleep satisfaction in ACS patients. The results of this study revealed placebo to be non-inferior to lorazepam for the evaluated cardiac events-chest pain, delirium, and arrhythmias. Trend of the result occurred at a higher delirium (4.0% *vs.* 1.6%, 95% CI 2.4% (-1.5% to 6.5%), $p \leq 0.001$ when to use t-test for non-inferiority test with 10% marginal) and arrhythmias (14.3% *vs.* 11.5%, 95% CI 2.8% (-4.3% to 9.9%), p=0.001) rates in the lorazepam group than in the placebo group. Lorazepam, although not listed in the American Heart Association (AHA) guidelines for the treatment of chest pain, is sometimes used to treat patients with chest pain in Emergency Departments (EDs) and inpatient settings. The anxiolytic effects of lorazepam can rapidly relieve symptoms of panic, and can reduce the anxiety associated with chest pain from any cause, which helps to avoid a pain-anxiety-pain cycle [9-11]. However, *causes* that may effectuate symptoms were tachycardia, rapid breathing or shortness of breath, restlessness, confusion, and mood changes. These lead to quit the sedation drug or change to another drug. Delirium complicates the hospital stay of more than 2-3 million elderly patients per year in the US and occurred in 80% of all patients and was the strongest predictor of length of stay in the hospital.

The authors' investigation in PCI group found that the differences between the drugs were not significant. In PCI group event rate occurred at a lower rate in the lorazepam group than in the placebo group and no PCI group had chest pain (16.1% *vs.* 10.3%) and arrhythmias (25.8% *vs.* 17.2%) higher rates in the lorazepam group of more than one. Percutaneous Coronary Intervention is standard treatment to relieve chest pain in acute coronary syndrome patients. However, the occurrence of chest pain in lorazepam group may be less. Because when drowsiness occurs after taking lorazepam, it leads to nurse intervention. Lorazepam may be useful in reducing chest pain. If the nurse inquires for more details, more information may be solicited.

Our sub analysis that compared diagnosis of STEMI with that of non-STEMI between study groups revealed no significant difference between groups. Lorazepam in patients with STEMI was less likely to cause chest pain than in patients with non-STEMI (1.0% *vs.* 4.2%). This may be due to STEMI patients receiving STEMI. Lorazepam in non-STEMI patients had chest pain (23.3% *vs.* 11.1%), delirium (13.3% *vs.* 3.7%), and arrhythmias (23.3% *vs.* 11.1%). Our study found that most STEMI patients were treated with PCI; therefore, lorazepam may not be effective in relieving chest pain or arrhythmias.

In this study, patients in the study group received lorazepam 0.5 mg once daily. The mean score of first-night sleep satisfaction was significantly higher in the lorazepam group than in the placebo group. Patient unfamiliarity with the critical care environment (e.g., medical equipment-related noise, bright lights, and conversation among staff) caused distraction and anxiety that made sleep difficult. However, on day 2, as the patients became familiar with their environment, they were able to sleep [12,13]. This finding suggests the efficacy of lorazepam in ACS patients to relieve anxiety and improve the quality of sleep during the first night of their hospital stay.

Lorazepam is given once daily in all acute coronary syndrome patients until the discharge of the patients. This is a long-standing treatment order. While studies have shown lorazepam is not beneficial in relieving chest pain or arrhythmias, it is possible that the patients are drowsy and do not realize chest pain. If patients are asked for more details, more information may be obtained. In contrast, there is some evidence that lorazepam is more likely to cause delirium. However,

lorazepam has an effect on sleep satisfaction score only in the first night of hospital stay.

Conclusion

Placebo was found to be non-inferior to lorazepam for the cardiac events evaluated in this study-chest pain, delirium, and arrhythmias. The mean score of first-night sleep satisfaction was significantly higher in the lorazepam group than in the placebo group, which suggests the efficacy of lorazepam in ACS patients to relieve anxiety and improve the quality of sleep during the first night of their hospital stay.

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References

1. Chang CC, Chen YC, Ong ET, Chen WC, Chang CH, et al. (2016) Chest pain after percutaneous coronary intervention in patients with stable angina. Clin Interv Aging 11: 1123-1128.
2. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, et al. (2018) 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 39: 119-177.
3. Melanie CR, Kevin FU, Ativan (lorazepam) (2016) College of Psychiatric and Neurological Pharmacists.
4. Honderick T, Williams D, Seaberg D, Wears RA (2003) A Prospective, Randomized, Controlled Trial of Benzodiazepines and Nitroglycerine or Nitroglycerine Alone in the Treatment of Cocaine-Associated Acute Coronary Syndromes. Am J Emerg Med 21: 39-42.
5. Sundström BW, Bång A, Karlsson T, Winge K, Lundberg C, et al. (2013) Anxiolytics in patients suffering a suspected acute coronary syndrome: Multi-centre randomised controlled trial in Emergency Medical Service. Int J Cardiol 168: 3580-3587.
6. Moser DK, Dracup K (1996) Is Anxiety Early After Myocardial Infarction Associated With Subsequent Ischemic and Arrhythmic Events? Psychosom Med 58: 395-401.
7. Breivik EK, Bjornsson GA, Skovlund E (2000) A comparison of pain rating scales by sampling from clinical trial data. Clin J Pain 16: 22-28.
8. Zartrungpak S, Prasertchai R, Jennawasin S, Saipanish R (2000) Thai Delirium Rating Scale. J Psychiatr Assoc Thailand 45: 325-332.
9. Marcantonio ER, Juarez G, Goldman L, Mangione CM, Ludwig LE, et al. (1994) The relationship of postoperative delirium with psychoactive medications. JAMA 272: 1518-1522.
10. Dubois MJ, Bergeron N, Dumont M, Dial S, Skrobik Y (2001) Delirium in an intensive care unit: a study of risk factors. Intensive Care Med 27: 1297-1304.
11. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, et al (2006) Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 104: 21-26.
12. Pandharipande P, Cotton BA, Shintani A, Thompson J, Pun BT, et al. (2008) Prevalence and risk factors of delirium in surgical and trauma intensive care unit patients. J Trauma 65: 34-41.
13. Delaney LJ, Haren FV, Lopez V (2015) Sleeping on a problem: the impact of sleep disturbance on intensive care patients - a clinical review. Ann Intensive Care 5: 3.