Full Length Research Paper

Morphine use in elderly patients with acute heart failure

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Morphine has been considered as an important medicine to treat acute heart failure (AHF) for a long time. This study was designed to explore the usage rate of morphine in emergency department and its influence on the prognosis of the elderly patients with AHF in china. A prospective investigation of elderly patients with AHF, who were treated and admitted from emergency room of the General Hospital of the People's Liberation Army (GHPLA) in China, were performed. The patients were divided into two groups: control group and morphine treatment group. The relationships between the usage of morphine and clinical factors such as demographic characters of patients and past history were analyzed. The effect of morphine on mechanical ventilation, hospitalization stay and the mortality of patients were also evaluated. The usage rate of morphine was 50% in the emergency room. The patients on the morphine treatment group were more likely to have past history of coronary heart disease, type 2 diabetes mellitus (T2DM) and stroke than those of the control group (p < 0.05). The patients on morphine treatment group had higher troponin-T values compared with those of the control group (p < 0.05). Morphine usage was not an independent risk factor of mortality (OR: 2.172, p: 0.187, 95% CI: 0.686 to 6.879). The Odd ratio of morphine usage for mechanical ventilation incidence was 3.01 (95%CI, 1.22 to 7.41). High prevalence of morphine usage was found in the elderly AHF patients from emergency room of GHPLA in China. Morphine is still a safe medicine in early treatment on the elderly patients with AHF with mechanical ventilation in China.

Key words: Morphine, acute heart failure, mechanical ventilation, mortality.

INTRODUCTION

Heart failure (HF) is a terminal stage of many cardiovascular diseases, including hypertension, myocardial infarction and valvular coronary disease. There were approximately 670,000 new cases of patients with HF per year in U.S (Horwich and Fonarow, 2010). It resulted in poor clinical outcomes, and five-year survival rate of the patients with HF is less than 50%. The patients with HF had high mortality and readmission (Demir et al., 2008; Saczynski et al., 2009), especially the mortality of those patients with acute heart failure (AHF) was as high as 15 to 24%

in hospital (Fonarow et al., 2005; Krumholz et al., 1997).Unfortunately, there were few data from controlled trials to guide the treatment of the patients with AHF.

Morphine has been considered as an important medicine to treat AHF for a long time. However, a number of controversial data have been published about its favorable or adverse effects on the heart. It was supposed to reduce heart rate, preload and afterload of heart, these effects may cause a reduction of cardiac oxygen demand, which was still lack of evidence support (Grimm, 2006). According to an analysis result of Acute Decompensated Heart Failure National Registry (ADHERE) (Peacock et al., 2008), a strong association was found between mechanical ventilation and the usage of morphine, but another retrospective study supported the association between the usage of morphine and a high in-hospital mortality (Mattu and Lawner, 2009;

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Bosomworth, 2008).

Morphine can apparently increase parasympathetic activity and suppress cardiovascular functions (Napier et al., 1999; Randich et al., 1991). Prolonged morphine administration and subsequent withdrawal can affect catecholamine turnover and thus myocardial adrenergic signaling and function (Chang and Dixon, 1990; Rabadan et al., 1997). So it might be important to differentiate between the consequences of short and long-term morphine application.

Previous study showed that one-shot administration of morphine to rats prior to a permanent coronary artery occlusion produced a statistically significant increase in infarct size (Markiewicz et al., 1982). However, several studies have been published in which a role of opioid receptors in morphine induced acute and delayed preconditioning was confirmed (Chen et al., 2008; Frassdorf et al., 2010; Gintzler and Chakrabarti, 2006; Jiang et al., 2006; McPherson and Yao, 2001; Peart et al., 2005; Shi et al., 2003; Zuurbier et al., 2005). In addition, cardioprotective effect of chronic morphine exposure has also been observed in a mouse model of myocardial infarction (Peart and Gross, 2004; Peart et al., 2011). Nowadays in China, many emergency physicians continue to use morphine as a medication to treat AHF. Because of the possibility that morphine can result in adverse outcomes, its future use for the patients with AHF should be reconsidered. Therefore, this study was designed to explore the usage of morphine in emergency department (ED) and its influence on the prognosis of the elderly patients with AHF in china.

MATERIALS AND METHODS

Clinical cases

A prospective observational analysis from medical records of consecutive patients, firstly treated in ED and then admitted in hospital between December 2008 and 2009, was performed. The clinical presentations, etiologies and treatments of the patients were evaluated. Initial diagnosis of AHF was established based on typical clinical symptoms and physical signs (Dickstein et al., 2008): acute dyspnea occurring at rest or orthopnea; pulmonary congestion detected during physical examination (generalized rales up to scapular angles); gallop rhythm; typical radiographic picture consisting of generalized pulmonary mottling; originating from pulmonary hilus; Brain natriuretic peptide (BNP) level > 400 pg/ml.

The standard of case selection

The diagnosis of AHF was confirmed during hospital stay by excluding other causes of dyspnea (especially respiratory disorders). All the diagnoses of the patients were supervised by two senior attending physicians from ED or cardiology department, those patients whose diagnosis disaccord were excluded. The patients with the history of longstanding usage of morphine and some consuming diseases, such as carcinoma at end stage and drug abuser were also excluded. After a patient was discharged or died in hospital. 82 cases of patients were enrolled in this study, 52 males and 30 females, aged from 65 to 99 years. The medical record was collected and divided into two groups: control group (n = 41) and morphine treatment group (n = 41) based on the usage of morphine in ED.

The method of clinical investigation

The relationship between the usage of morphine and clinical factors such as demographic characters, past medical history, initial presentations and medications of the patients were analyzed. The effects of morphine on mechanical ventilation, hospitalization stay and in-hospital mortality were also evaluated.

Statistical analysis

The continuous variables were expressed as mean ± standard deviation or median (Q1, Q3). Differences in gerontology, etiology and clinical factors between elderly patients from the two groups in ED were assessed using student-'t', Mann-Whitney U and X^2 tests. Risk factors were identified by using Binary logistic regression analysis, P value < 0.05 was considered statistically significant.

RESULTS

Demographic characteristics and past history of the elderly AHF patients

As shown in Table 1, no gender and age differences were found between the patients on the two groups. Etiologic factors included coronary artery disease (CHD), hypertension, prior heart failure, hyperlipidemia, chronic kidney disease (CKD), type 2 diabetes mellitus (T2DM), chronic obstructive pulmonary disease (COPD) and cerebral stroke. A higher incidence of CHD, T2DM and cerebral stroke were found in patients with the usage of morphine.

The safety of morphine on initial presentations of elderly AHF patients

As shown in Table 2, higher troponin-T and random blood glucose values were found in morphine group. No differences were found in values of the factors [blood urea nitrogen (BUN), systolic blood pressure (SBP) and creatinine (Cr)] that were always considered as the predictors of mortality between the patients of two groups. The BNP level of the patients on morphine treatment group was higher compared with that of the patients on the control group but the difference was not statistically significant. Since morphine usage is correlated to troponin-T elevation as shown in Table 2, we further evaluated stratified OR of morphine usage for mechanical ventilation incidence by addition of factors such as, hyperglycemia, troponin-T elevation, raised white blood cell (WBC) counts, vasodilators and diuretics. The binominal logistic regression showed the addition of other factors changed the power of morphine usage on mechanical ventilation incidence. Morphine usage was not an independent risk factor of mortality (OR: 2.172,

Table 1. Demography and past medical history of elderly ADHF patients with or without the treatment of morphine in ED.

Parameter	Patients with morphine usage in ED (n=41)	Patients without morphine usage in ED (n=41)	P
Demography			
Age (years)	78.17±7.283	77.37±7.522	0.624
Gender (male)	25	27	0.647
Past medical history			
Coronary Heart Disease	39	29	**0.003**
Prior Heart Failure	28	30	0.355
Hypertension	34	32	0.577
Chronic kidney disease	21	19	0.517
Diabetes	28	16	**0.008**
Hyperlipidemia	27	21	0.179
COPD	14	17	0.494
Cerebral stroke	18	7	**0.008**

Age is reported as mean ± SD, the other variables are reported by number of cases.

Table 2. Initial presentations of elderly ADHF patients with or without the treatment of morphine.

Parameters	Patients with morphine usage in ED (n=41)	Patients without morphine usage in ED (n=41)	P
Initial presentations			
Body mass index	24.87 (21.25, 28.35)	23.67 (20.03, 26.30)	0.141
Breathe (min^{-1})	24 (19, 29)	22 (19, 28)	0.732
Heart rate (beats/min)	108 (78, 127)	90 (80, 118)	0.257
SBP (mmHg)	140 (119, 167)	140 (116, 151)	0.724
DBP (mmHg)	78 (64, 86)	80 (60, 90)	0.654
PaO$_2$ (mmHg)	72.5 (60.9 99.7)	77.8 (59.5, 93.9)	0.466
PaCO$_2$ (mmHg)	35.3 (29.5, 42.5)	33.8 (28.9, 40.0)	0.810
pH	7.38 (7.29, 7.42)	7.39 (7.30, 7.43)	0.424
BUN (mmol/L)	11.2 (7.8, 15.7)	11.0 (6.4, 19.6)	0.795
Cr (μmol/L)	117.9 (74.9, 230.0)	102.7 (75.6, 163.6)	0.706
GPT (U/L)	24.9 (15.3, 46.8)	20.8 (15.1, 47.3)	0.664
GOT (U/L)	32.3 (23.0, 46.0)	30.2 (23.0, 57.9)	0.885
BNP (pg/ml)	9616.0 (2129.5, 18848.5)	3294.5 (1092.3, 9743.3)	**0.070**
cTnt (μg/L)	0.317 (0.044,1.270)	0.038 (0.010,0.220)	**0.008**
RBG (mmol/L)	9.02 (7.19, 13.29)	7.31 (5.56, 11.03)	**0.050**
Uric Acid (μmol/L)	342.4 (252.9, 465.8)	402.9 (265.2, 466.1)	0.791
RBC (×10^{12}/L)	3.52 (3.05, 4.27)	3.84 (3.29, 4.59)	0.235
WBC(×10^9/L)	9.35 (6.98, 13.55)	8.58 (6.51, 12.48)	0.519
PLT(×10^9/L)	182.0 (137.5, 229.0)	168.0 (137.5, 240.5)	0.893
Hb (g/L)	117.0 (94.5, 136.5)	118.0 (93.5, 138.0)	0.777
D-Dimer (mg/dL)	1.44 (0.55, 3.16)	2.01 (0.87, 3.45)	0.242
CRP(mg/dL)	3.7 (0.6, 7.3)	2.52 (0.70, 8.80)	0.882
EF	0.53 (0.45, 0.58)	0.55 (0.44, 0.60)	0.613

All continuous variables were expressed as medium (Q1, Q3). GOT: glutamic oxaloacetic transaminase; GPT: glutamate-pyruvate transaminase; BUN: blood urea nitrogen; Cr: creatinine; BNP: brain natriuretic peptide; cTnt: cardiac troponin-T; RBG: Random blood glucose; RBC: red blood cell; WBC: white blood cell; Hb: hemoglobin; PLT: platelet; CRP: C reactive protein; EF: ejection fraction.

p: 0.187, 95% CI: 0.686 to 6.879).

The effect of morphine treatment on the patients at early stage of AHF

In order to evaluate the effect of morphine treatment on the patients on early stage of AHF in ED, as shown in Table 3, we recorded all medications used before morphine application in ED. A further analysis revealed a strong relationship between theophylline and morphine. Intravenous diuretics, vasodilators and inotropes were administrated on same levels in two groups.

The effect of morphine on the in hospital outcomes of elderly patients

As shown in Table 4, we set mechanical ventilation, prolonged hospitalization stay and mortality as indicators of in-hospital outcomes to examine adverse effects of morphine usage in elderly AHF patients. The patients who received the treatment of morphine did have higher incidence of mechanical ventilation, but no difference of mortality and hospitalization stay was found between the patients of the two groups.

The clinical factors affecting the incidence of mechanical ventilation

The incidence of mechanical ventilation was also influenced by many clinical factors other than morphine. We analyzed all clinical factors mentioned above to determine the risk factors of mechanical ventilation including morphine. The results showed that hyperglycemia, troponin-T elevation raised WBC counts, and morphine were correlated to mechanical ventilation rate. The Odd ratio of morphine usage for mechanical ventilation incidence was 3.01 (95% CI, 1.22 to 7.41) Vasodilators and Diuretics were related to the decreased mechanical ventilation incidence (Table 5).

DISCUSSION

Morphine is a commonly accepted therapy treatment in patients with AHF. A newly published guideline of AHF treatment in China recommends the usage of morphine on early stage of AHF management (Jun, 2010). The 2005 European Task Force guideline of AHF treatment as well as the 2008 guideline also continue to recommend intravenous injection of morphine during AHF treatment. For many years, morphine has been considered to have the effects of anti-anxiety and vasodilatation (Timmis et al., 1980) and is used as a conventional medication of AHF but morphine also has

side effects of respiratory depression and adverse hemo-dynamic effect that can cause myocardial depression (Sumida et al., 2009; Kanaya et al., 1998). The safety and efficacy of morphine usage in AHF treatment has been questioned in recent years. Different clinical trials revealed conflict effects of morphine on clinical outcomes of AHF patients (Johnson, 2009; Sosnowski, 2008)

This study was a prospective observational cohort study of morphine usage in elderly AHF patients in China. The results showed that much higher morphine usage prevalence in the ED of a Chinese hospital than that of ADHERE analysis (50% vs. 14.1%) (Peacock et al., 2008). In China, most physicians still hold the view of morphine as a useful preload reducing and anxiolytic medication. The 2010 guidelines of AHF treatment designed by Chinese Medical Association also approved the application of morphine in early stage of acute heart failure symptomatic treatment (Jun, 2010). There is no literature that reported morphine usage prevalence in elderly AHF patients in Chinese hospitals before, the result of this study may reflect the reality of high morphine usage in AHF manage-ment in Chinese emergency departments.

This study suggested the patients with the treatment of morphine were more likely to have medical history of coronary heart disease, T2DM and stroke compared with the other group. We believe a history of arteriosclerosis related diseases may influence the decision making of physician in ED to give patient morphine as sedative medication by assuming a possible myocardial ischemia. The linkage of myocardial ischemia and morphine usage is also suggested by higher troponin-T values in patients on morphine than the patients who did not received the treatment of morphine. We hypothesized that some physi-cians in ED used morphine as analgesic for angina other than medication of AHF. Unfortunately, in this study this aspect was not recorded on the purpose of morphine usage in ED to test this hypothesis.

Since the possible replacement of morphine such as benzodiazepine also has side effects of respiratory depression, morphine is a considerable choice when vasodilators and diuretics cannot control symptoms of AHF effectively. Our study found that most patients had been given intravenous theophylline before the treatment of morphine. The reason of this phenomenon may be that physicians in ED tended to give theophylline to rule out possible non-cardiac dyspnea before the administration of morphine.

This study showed a higher in-hospital mortality (39.0% in morphine group and 36.6% in non morphine group) compared with the results of ADHERE analysis (13.0% in morphine group and 2.4% in non morphine group), the possible reason may be advanced age and advanced degree of HF. We could not find statistic difference of the mortality of the patients between two groups. In this study, some factors (BUN, SBP and Cr) that are commonly considered as the predictors of mortality were similar between the patients on the two groups and the levels of

Table 3. Medications before morphine usage of elderly ADHF patients in ED

Parameters	Patients with morphine usage in ED (n=41)	Patients without morphine usage in ED (n=41)	P
Intravenous medications			
Vasodilators	38	32	0.061
Inotropes	19	22	0.742
Diuretics	39	34	0.077
Theophylline	27	15	**0.008**
Steroids	15	10	0.175

All variables were expressed as number of cases.

Table 4. In hospital outcomes of elderly patients with or without the treatment of morphine.

Parameters	Patients with morphine usage in ED (n=41)	Patients without morphine usage in ED (n=41)	P
In hospital outcomes			
Mechanical ventilation	25	14	0.015
Hospital stay (days)	15 (6, 21)	14 (7, 25)	0.957
In-hospital mortality	16	15	0.820

Hospital stay were expressed as medium (Q1, Q3), the other variables were expressed as number of cases.

Table 5. Factors related to mechanical ventilation.

Parameters	Patients received mechanical ventilation (n=39)	Patients not received mechanical ventilation (n=43)	P	OR
Hyperglycemia	30	22	0.016	3.29
cTnt elevation	25	17	0.024	2.98
Raised WBC counts	22	14	0.030	2.68
Vasodilators	30	40	0.039	0.25
Diuretics	32	41	0.054	0.223
Morphine	25	16	0.015	3.013

Variables were expressed as number of cases; Hyperglycemia: RBG > 7.1mmol/l; cTnt elevation: troponin-T > 0.1 μg/l; Raised WBC counts: WBC > 10.0×10^9/L.

BNP, random blood glucose (RBG) and troponin-T were higher in morphine treatment group. At the end of this study, the patients who received the treatment of morphine had the similar mortality with their counter parts.

Intravenous morphine was used in 50% elderly hospitalized patients with AHF in this study. A marked increase of mechanical ventilation usage was observed in the patients on morphine treatment group. But the power of morphine usage on mechanical ventilation incidence was diminished after stratification of other mechanical ventilation related risk factors. Further binominal logistic regression showed morphine usage was not an independent risk factor of mortality. In this study, prolonged hospitalization stay was not found in the patients on morphine treatment group which was found in an article of ADHERE analysis could not found (Peacock et al., 2008). In this study, the mean length of hospitalization stay in both groups was about 2 weeks, which was much longer than that of ADHERE analysis (5.6 days in morphine group and 4.2 days in non morphine group). The effect of morphine on length of hospitalization stays maybe diminished by such a long stay.

Conclusion

This study is the first prospective cohort study on morphine usage in elderly AHF patients in China. The results suggested that morphine was still a safe medicine in early stage of treatment of elderly AHF patients in Chinese hospitals with mechanical ventilation support. But it was only a study with small sample and its conclusion still need to be confirmed by more prospective clinical trials with large scale.

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