Journal of Clinical & Experimental Cardiology

Guo et al., J Clin Exp Cardiolog 2017, 8:9
DOI: 10.4172/2155-9880.1000538

Review Article OMICS International

Early Intravenous Beta-blockers for Acute Myocardial Infarction

Shu Hong Guo, Yi He and Qiang Fu*

Cardiovascular Department, Zhuzhou Central Hospital, Zhuzhou 412007, China

***Corresponding author:** Qiang Fu, Cardiovascular Department, Zhuzhou Central Hospital, Zhuzhou 412007, China, Tel: 8615570728025; E-mail: 243587581@qq.com

Received date: August 16, 2017; **Accepted date:** September 05, 2017; **Published date:** September 12, 2017

Abstract

Early intravenous beta-blockers reduce the risk of recurrent ischaemia and ventricular arrhythmia in the treatment of acute myocardial infarction. These beneficial efficacy, however, are balanced by a high rate of cardiogenic shock. It has great significance for reliable identification of subgroups of patients among whom treatment is really advantageous. The present article is a review on the efficacy and safety of the early intravenous beta-blockers, and provides an evaluation procedure to guide clinicians applying intravenous beta-blockers to clinical practice.

Keywords Beta-blockers; Acute myocardial infarction

Review

Beta-blockers are heralded as a major advance in the treatment of patients with myocardial infarction (MI). Patients without contraindications are recommended to receive intravenous administration of beta-blockers at the time of presentation for relief of ischemic pain; for the control of hypertension, sinus tachycardia and sustained ventricular tachycardia; and for the primary prevention of sudden cardiac death (Class I, Level of Evidence B) [1]. Recent data have called into question the role of beta-blockers in MI. Recommendations on the intravenous administration of beta-blockers by current guidelines are more prudent in these cases (Class IIa, Level of Evidence B) [2,3]. The use of early β-blocker therapy for patients with AMI in China is suboptimal, with underuse in patients who could benefit and substantial use among those who might be harmed [4]. The present article is a review on the efficacy and safeties of the early administration of intravenous beta-blockers examined in trials conducted in the pre-reperfusion era and reperfusion era, and provide an evaluation procedure to guide clinicians applying IV beta-blockers to clinical practice.

Death

Two large trials were conducted in the pre-reperfusion era. In the Metoprolol in Myocardial Infarction (MIAMI) trial, intravenous metoprolol followed by oral administration did not significantly reduce 15-day mortality (4.3% *vs.* 4.9%, P=0.29) as compared to placebo [5]. In another large randomized study, the First International Study of Infarct Survival (ISIS-1) trial, there was significantly lower vascular mortality during the first seven days in the atenolol group (3.89% *vs.* 4.57% , P<0.04) as compared to the placebo group [6]. A meta-analysis of 51 early trials of intravenous beta-blockers, administered at the time of presentation in the pre-reperfusion era, revealed a small and non-significant reduction in mortality. The number needed to treat (NNT) was 250 patients to avoid one death [7].

Similarly, two large trials were conducted in the reperfusion era. In the Thrombolysis in Myocardial Infarction (TIMI) Phase IIB study, there was no difference in mortality neither within 6 days of entry (2.4% *vs.* 2.4%, P=0.98) nor within 6 weeks of entry (3.6% *vs.* 3.5%, P=0.91) between the immediate metoprolol intravenous and deferred groups [8]. The ClOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) were to assess the balance of risks and benefits of adding early intravenous then oral metoprolol to standard therapies in a wide range of patients. For death alone, there were 1774 deaths in the metoprolol group versus 1797 in the placebo group (7·7% *vs.* 7·8%, p=0·69) [9]. Recent meta-analysis showed that intravenous beta-blockers have no mortality benefit in the current reperfusion era [10-12]. As a whole early short term intravenous beta-blockers immediately after acute myocardial infarction (AMI) seems unlikely to be of major benefit in reducing mortality in the reperfusion era.

Ventricular Arrhythmia and Recurrent Ischaemia

The MIAMI trial indicated that intravenous metoprolol had no significant effect on ventricular fibrillation but the number of episodes tended to be lower in the metoprolol treated patients during the later phase (6-15 days; 24 *vs.* 54). Fewer recurrent infarctions (3.0% *vs.* 3.9%, P=0.08) in the metoprolol group were recorded as compared to the placebo group [5]. The ISIS-1 trial reported a non-significant fewer non-fatal cardiac arrest (2.4% *vs.* 2.5%, P>0.05) and non-significant re-infarction (2.5% *vs.* 2.8%, P>0.05) between the atenolol group and placebo group [6]. In the TIMI IIB trial, there was a lower incidence of re-infarction (2.7% *vs.* 5.1%, p=0.02) and recurrent chest pain (18.8% *vs.* 24.1%, p<0.02) in the immediate metoprolol intravenous group as compared to the deferred group [8]. In the COMMIT trial, allocation to metoprolol was associated with five fewer people having re-infarction (2·0% *vs.* 2·5%; p=0·001) and five fewer people having ventricular fibrillation (2·5% *vs.* 698 3·0%; p=0·001) per 1000 treated. The reduction in re-infarction and ventricular fibrillation emerged more gradually [9]. Overall, early intravenous beta-blockers immediately after AMI was associated with reduction in ventricular arrhythmia and re-infarction both in the pre-reperfusion era [6] and reperfusion era [10-12].

Infarct Size and Left Ventricular Ejection Fraction (LVEF)

In TIMI IIB trial, metoprolol therapy was selected to improve resting LVEF in patients receiving recombinant tissue Plasminogen Activator (rt-PA), less than 4 h after the onset of symptoms. Global

LVEF was similar in the patients assigned to immediate and delayed metoprolol therapies [8]. Ibanez et al. reported that, in patients with anterior Killip class II or less ST-Elevation Myocardial Infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI), early intravenous metoprolol before reperfusion reduced infarct size and increased LVEF with no excess of adverse events [13]. This beneficial effect on infarct size and LVEF; however, was not demonstrated in another similar designed study [14]. A recent meta-analysis of four trails only enrolled patients with confirmed STEMI with symptoms lasting less than 6 or less than 12 h concluded that intravenous beta-blockers in conjunction with PCI are associated with improved LVEF at 24 weeks in STEMI patients presenting in Killip Class 1 or 212.

Cardiogenic Shock

Information on cardiogenic shock was not collected systematically in most of the trials in the pre-reperfusion era, which included a small number of fairly low-risk patients. In the MIAMI trial, intravenous metoprolol did not increase cardiogenic shock (3.0% *vs.* 3.2%, P>0.20) as compared to placebo [5]. No information on cardiogenic shock were recorded in the ISIS-1 trial, which only revealed that atenolol use increased the extent of inotropic drug use (5.0% vs 3.4%, p<0.0001), chiefly on days 0 and 16. In the reperfusion era, the COMMIT trial indicated that there was more developing cardiogenic shock per 1000 persons (5·0% *vs.* 3·9%; p<0.00001) allocated to metoprolol group, especially on days 0 and 19. In a Swedish nationwide observational study, the use of intravenous beta-blockers in STEMI patients without cardiogenic shock and cardiac arrest at presentation treated with primary PCI was associated with higher short-term mortality, lower LVEF at discharge, as well as a higher risk of in-hospital cardiogenic shock [14,15]. While recent meta-analysis concluded that early use of intravenous beta-blockers in STEMI patients presenting in Killip Class 1 or 2 was not associated with increase in the risk of cardiogenic shock in the current reperfusion era [11,12].

Which Type of Patients Might Really Benefit?

Overallearly intravenous beta-blockers followed by high-dose oral therapy reduced recurrent ischaemia and ventricular arrhythmia at the expense of increased cardiogenic shock and the extent of inotropic drug use. As such, it has great significance for reliable identification of subgroups of patients among whom treatment is really advantageous.

Of the total vascular deaths within 14 days in the ISIS-1trial, 43.6% occurred in the first two days. Most of the improvement in vascular mortality was seen during days 0 and 1, inferring that early intravenous beta-blockers therapy might mainly benefit higher mortality risk patients [6]. In the MIAMI study, a retrospective subgroup analysis indicated that all the observed reduction in mortality was among the intravenous metoprolol treated patients defined as being at higher mortality risk [5]. A completely opposite conclusion drawn from the TIMI II-B trial indicated that immediate metoprolol therapy was beneficial only in patients in the low risk subgroup but did harm to patients in the not-low-risk subgroup. An explanation for this controversy is that the pre- and in-hospital management has changed a lot since the pre-reperfusion era. Patients received timely revascularization and optimal drug therapy nowadays, which reduces the likelihood of extensive scar formation, a vital substrate for re-entrant circuits and fatal ventricular arrhythmias, which might neutralize the good impact of beta-blockers [8]. In COMMIT trial, there was a tendency towards net benefit in those at lower risk of developing cardiogenic shock. Patients presenting lower systolic blood pressure (≤120 mmHg), higher heart rate (≥90 bpm), worse Killip class (≥ III); and patients receiving no fibrinolytic agent and/or having long delay time to reperfusion were at high risk of developing cardiogenic shock, especially in the elderly ≥70 years old [9].

How to Identify Eligible Patients?

In the pre-reperfusion era, Hands et al. reported that cardiogenic shock developed in 7.1% of 845 patients admitted with AMI. In half of these patients, cardiogenic shock developed at least 24 h after hospital admission. Independent predictors of the occurrence of cardiogenic shock were age (>65 years), LVEF on hospital admission (<35%), large infarct as estimated from serial enzyme determinations, history of diabetes mellitus and prior MI. Patients with three, four, or five of these risk factors had a 17.9%, 33.7%, or 54.4% probability, respectively, of developing cardiogenic shock after hospital admission. In this study, parameters from the physical examination were not included in the analysis [16]. In the reperfusion era, a scoring system algorithm was developed to predict the occurrence of cardiogenic shock among 41,021 patients with AMI receiving thrombolytic therapy in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries-I (GUSTO-I) trial and validated in the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO-III) cohort. In this algorithm, age, heart rate, systolic blood pressure, diastolic blood pressure, weight, MI location, Killip Class and miscellaneous risk factors such as female, hypertension and prior MI were all predictors for the development of cardiogenic shock after thrombolytic therapy. Among these predictors, age, systolic blood pressure, heart rate and Killip class were the four major predictive variables which accounted for greater than 85% of the predictive information. In the GUSTO-I trial, the median time from enrollment to cardiogenic shock was 11.6 h, 39.6% cardiogenic shock occurring within 6 hours, and 63.2% within 24 h [17]. Physical examination such as altered sensorium, oliguria and cold clammy skin were also of great significance in recognizing cardiogenic shock [18].

Rahimi et al. reported that 2.6% of 588 patients admitted with Non-ST-Elevation Myocardial Infarction (NSTEMI) developed ventricular arrhythmias. In addition, more than two-thirds of arrhythmias occurred within the first 12 h after onset of symptoms. Moreover, the only factor associated with the occurrence of malignant ventricular arrhythmia was higher white blood cell count on admission [19]. A similar study of 510 patients who underwent PCI for STEMI indicated that 60% of sustained ventricular arrhythmia occurred during the first 24 h, and 92% during the first 48 h. Independent predictors of sustained ventricular arrhythmia included higher white blood cell count, lower hematocrit and lack of beta-blocker medication [20,21]. Overall, the occurrence of ventricular arrhythmias after AMI was not easy to predict. An electrocardiographic monitoring period of 48 h may be helpful in timely detection of ventricular arrhythmia based on the arrhythmia onset time window. Electrocardiogram information such as fragamented QRS wave21, QT interval prolongation [22,23], QT dispersion [24,25], T-wave alternans (TWA) and late potentials (LP) [26], reduced heart rate variability (HRV) [27] and R-on-T phenomenon [28] were demonstrated some value for predicting ventricular arrhythmia in patients with AMI. Also of great assistance in predicting ventricular arrhythmia were predictors such as left ventricular ejection fraction [29] and hapokalemia [30]. There was,

however, no such scoring system algorithm as predicting cardiogenic shock.

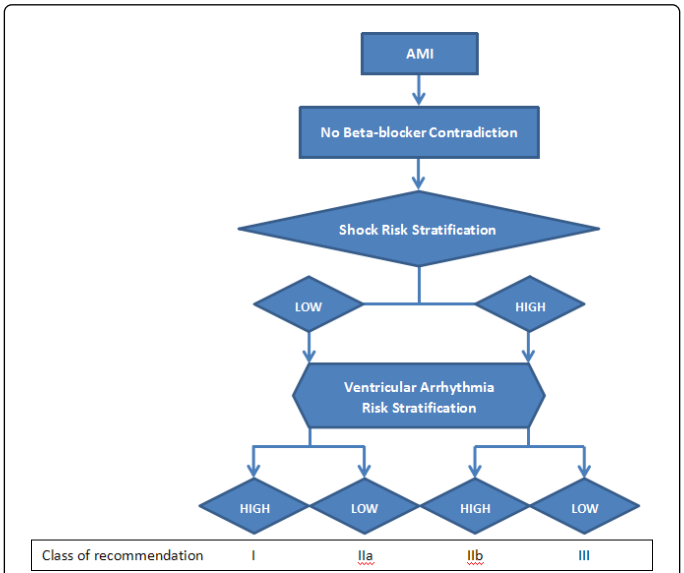

Figure 1: Evaluation procedure and class of recommendation of intravenous beta-blockers for acute myocardial infarction.

Taking the efficacy and the safety into account, it may be reasonable to intravenously administer beta-blockers in those patients at low risk of developing cardiogenic shock for its beneficial effect on reducing life-threatening arrhythmia and relieving recurrent ischemia. For patients at higher risk of developing cardiogenic shock, early intravenous beta-blockers (Figure 1) may be potentially harmful. In such a case early emergency revascularization of occluded coronaries should be the primary treatment of choice [3].

References

1. López-Sendón J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, et al. (2005) Expert Consensus document on beta-adrenergic receptor blockers. Rev Esp Cardiol 58: 65-90.
2. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC)1, Steg PG, James SK, Atar D, Badano LP, et al. (2012) ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 33: 2569-2619.
3. O'Gara PT, Kushner FG, Ascheim DD (2013) ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines: developed in collaboration with the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv 82: E1-27.
4. Zhang H, Masoudi FA, Li J (2015) National assessment of early ß-blocker therapy in patients with acute myocardial infarction in China, 2001-2011: The China Patient-centered Evaluative Assessment of Cardiac Events (PEACE)-Retrospective AMI Study. Am Heart J 170: 506-515.
5. Held PH (1985) Metoprolol in acute myocardial infarction. Mortality. The MIAMI Trial Research Group. Am J Cardiol 56: 15G-22G.
6. Held PH (1986) Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group. Lancet 2: 57-66.
7. Freemantle N, Cleland J, Young P, Mason J, Harrison J (1999) Beta Blockade after myocardial infarction: systematic review and meta regression analysis. BMJ 318: 1730-1737.
8. Roberts R, Rogers WJ, Mueller HS, Lambrew CT, Diver DJ, et al. (1991) Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) II-B Study. Circulation 83: 422-437.
9. Chen ZM, Pan HC, Chen YP, Peto R, Collins R, et al. (2005) Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 366: 1622-1632.
10. Bangalore S, Makani H, Radford M, Thakur K, Toklu B, et al. (2014) Clinical outcomes with Î²-blockers for myocardial infarction: a meta-analysis of randomized trials. Am J Med 127: 939-953.
11. Elgendy IY, Elgendy AY, Mahmoud AN, Mansoor H, Mojadidi MK, et al. (2016) Intravenous ß-blockers for patients undergoing primary percutaneous coronary intervention: A meta-analysis of randomized trials. Int J Cardiol 223: 891-897.
12. Sterling LH, Filion KB, Atallah R, Reynier P, Eisenberg MJ (2017) Intravenous beta-blockers in ST-segment elevation myocardial infarction: A systematic review and meta-analysis. Int J Cardiol 228: 295-302.
13. Ibanez B, Macaya C, Sánchez-Brunete V, Pizarro G, Fernández-Friera L, et al. (2013) Effect of early metoprolol on infarct size in ST-segment-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial. Circulation 128: 1495-1503.
14. Roolvink V, Ibáñez B, Ottervanger JP, Pizarro G, van Royen N, et al. (2016) Early Intravenous Beta-Blockers in Patients With ST-Segment Elevation Myocardial Infarction Before Primary Percutaneous Coronary Intervention. J Am Coll Cardiol 67: 2705-2715.
15. Mohammad MA, Andell P, Koul S, Desta L, Jernberg T, et al. (2017) Intravenous beta-blocker therapy in ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention is not associated with benefit regarding short-term mortality: a Swedish nationwide observational study. EuroIntervention 13: e210-e218.
16. Hands ME, Rutherford JD, Muller JE (1989) The in-hospital development of cardiogenic shock after myocardial infarction: incidence, predictors of occurrence, outcome and prognostic factors. The MILIS Study Group. J Am Coll Cardiol 14: 40-46.
17. Hasdai D, Califf RM, Thompson TD, Hochman JS, Ohman EM, et al. (2000) Predictors of cardiogenic shock after thrombolytic therapy for acute myocardial infarction. J Am Coll Cardiol 35: 136-143.
18. Menon V, Hochman JS (2002) Management of cardiogenic shock complicating acute myocardial infarction. Heart 88: 531-537.
19. Rahimi K, Watzlawek S, Thiele H, Secknus MA, Hayerizadeh BF, et al. (2006) Incidence, time course, and predictors of early malignant ventricular arrhythmias after non-ST-segment elevation myocardial infarction in patients with early invasive treatment. Eur Heart J 27: 1706-1711.
20. Ohlow MA, Geller JC, Richter S, Farah A, Müller S, et al. (2012) Incidence and predictors of ventricular arrhythmias after ST-segment elevation myocardial infarction. Am J Emerg Med 30: 580-586.
21. Das MK1, Maskoun W, Shen C, Michael MA, Suradi H, et al. (2010) Fragmented QRS on twelve-lead electrocardiogram predicts arrhythmic events in patients with ischemic and nonischemic cardiomyopathy. Heart Rhythm 7: 74-80.
22. Schwartz PJ, Wolf S (1978) QT interval prolongation as predictor of sudden death in patients with myocardial infarction. Circulation 57: 1074-1077.
23. Taylor GJ, Crampton RS, Gibson RS, Stebbins PT, Waldman MT, et al. (1981) Prolonged QT interval at onset of acute myocardial infarction in predicting early phase ventricular tachycardia. Am Heart J 102: 16-24.
24. Day CP, McComb JM, Campbell RW (1990) QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. Br Heart J 63: 342-344.

25. Higham PD, Furniss SS, Campbell RW (1995) QT dispersion and components of the QT interval in ischaemia and infarction. Br Heart J 73: 32-36.
26. Ikeda T, Sakata T, Takami M, Kondo N, Tezuka N, et al. (2000) Combined assessment of T-wave alternans and late potentials used to predict arrhythmic events after myocardial infarction. A prospective study. J Am Coll Cardiol 35: 722-730.
27. Cripps TR1, Malik M, Farrell TG, Camm AJ (1991) Prognostic value of reduced heart rate variability after myocardial infarction: clinical evaluation of a new analysis method. Br Heart J 65: 14-19.
28. El-Sherif N, Myerburg RJ, Scherlag BJ, Befeler B, Aranda JM, et al. (1976) Electrocardiographic antecedents of primary ventricular fibrillation. Value of the R-on-T phenomenon in myocardial infarction. Br Heart J 38: 415-422.
29. Odemuyiwa O, Malik M, Farrell T, Bashir Y, Poloniecki J, et al. (1991) Comparison of the predictive characteristics of heart rate variability index and left ventricular ejection fraction for all-cause mortality, arrhythmic events and sudden death after acute myocardial infarction. Am J Cardiol 68: 434-439.
30. Podrid PJ (1990) Potassium and ventricular arrhythmias. Am J Cardiol 65: 33E-44E.