

Bolus - only versus bolus followed by infusion of glycoprotein IIb/IIIa inhibitors during primary percutaneous coronary intervention

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Abstract

Background: Several randomized trials performed in the era of original glycoprotein inhibitors (GP IIb/IIIa) showed a reduction in major adverse cardiac events when compared with placebo in a wide variety of percutaneous coronary intervention (PCI) settings.

Methods: This prospective study included 100 consecutive patients with acute ST segment elevation myocardial infarction within 12 hr of onset of symptoms. All patients underwent primary PCI and were divided into two groups; Group 1 who received bolus plus infusion and group 2 who received bolus only GP IIb/IIIa inhibitors in the setting of PPCI. In-hospital mortality, reinfarction, bleeding and stroke were reported in all patients. **Results:** Primary end point was reported in 54% of patients in group 1 Vs 38% in group 2 ($p=0.108$), minor bleeding occurred in 12% of all patients (18% versus 6% in group 1,2 respectively, $P=0.065$), major bleeding occurred in 1% of all patients (2% versus 0% in group 1,2 respectively, $P=0.315$). **Conclusion:** The results of the current study suggest that bolus-only GPI is not inferior to bolus followed by 24- hours infusion as regard short term outcome with a trend for fewer mortality and bleeding complication rate.

Key words: STEMI, GPI, Coronary intervention

{**Citation:** Mohamed Salem, Amr Hamed, Shaimaa Moustafa, Ahmed Ramzy, Saad Ammar. Bolus - only versus bolus followed by infusion of glycoprotein IIb/IIIa inhibitors during primary percutaneous coronary intervention. American Journal of Research Communication, 2015, 3(9): 59-72} www.usa-journals.com, ISSN: 2325-4076.

Introduction

Platelet aggregation has a central role in patients with ST segment elevation myocardial infarction (STEMI) ⁽¹⁾. Glycoprotein inhibitors (GPI) are beneficial in reducing ischemic complications in patients undergoing PCI ⁽²⁾. Several randomized trials performed in the era of original GPI showed a reduction in major adverse cardiac events (MACE) of death, myocardial infarction (MI), and urgent revascularization by 35% to 50% when compared with placebo in a wide variety of PCI settings ^(3,5). Traditionally, GPI are administered as intravenous bolus followed by a prolonged 12 to 18 hours infusion ⁽²⁾. However, this regimen may be associated with increased vascular/bleeding complications and increased cost ^(4,6). Contemporary PCI practice has improved from the era of original GPI studies⁽⁷⁾. Novel interventional techniques, procedural equipments, routine stenting, and thienopyridine preloading with high dose of clopidogrel (600 mg) have reduced MACE⁽⁸⁾. Furthermore, emergent therapeutic alternatives to GPI including direct thrombin inhibitors like bivalirudin with short duration of infusion during the procedure only may offer the same clinical benefit with lower bleeding complications⁽⁹⁾. Therefore, it seems that elimination of GPI infusion may reduce bleeding complications while maintaining their efficacy in reducing the ischemic end points. In this prospective study, we tested safety and efficacy of bolus only versus bolus plus infusion of GPI during PPCI

Patients and methods

Study design

This prospective, controlled, non-randomized study enrolled 100 consecutive patients with acute STEMI. The study was done at the National Heart Institute, Cairo, Egypt in the period from January 2014 to August 2014. All patients were treated with primary PCI (PPCI). We aimed to explore safety and efficacy of bolus only versus bolus plus infusion of Glycoprotein IIb/IIIa inhibitors during PPCI. All patients signed an informed consent and the study was approved by the local ethics committee. Key inclusion criteria were: Patients who were presented within 12 hours from the onset of symptoms with a new, or presumed new ST segment elevation in 2 or more contiguous leads of at least 2mm in leads V2-V3 or 1mm in other leads or those with new LBBB. Key exclusion criteria were: > 12 hours from symptom onset, patients with contraindication to prolonged dual antiplatelet therapy (DAPT), and patients with hepatic or renal diseases.

Methods

Baseline evaluation

All patients had review of their medical history on admission to emergency department including analysis of demographic data (age, sex), presence of risk factors of coronary atherosclerosis, associated comorbidities, general and cardiac examination, 12 leads ECG which was performed immediately on admission and every 6 h during the first 24 h, and once daily until discharge, routine laboratory investigations including cardiac biomarkers (Troponin I & CK-MB).

Coronary angiography and PPCI

Aspirin (300 mg loading, then 75 mg maintenance) and clopidogrel (600 mg loading, then 150 mg/day maintenance for one week, then 75 mg/day for one year) were given on

admission and after PPCI. Un-fractionated heparin (UFH) of 10000 units bolus dose was given after sheath insertion. The procedure was done according to the standard technique for coronary angiography and PCI. Transfemoral approach was done in all patients by using 6 Fr sheaths. Diagnostic coronary angiography was done to explore non-infarct related artery. XB or Judkin left guide catheters were used during PPCI in left system, while Judkin right catheter in RCA. Aspiration catheters were used in lesions with heavy thrombus burden and or impaired TIMI flow after PPCI. Bare metal stents were used in all patients. The operator determined the size, length of the stent. Sheaths were removed 4-6 hours after the procedure or 4 hours after stop of GPI infusion.

Dose regimen of GPI

After diagnostic coronary angiography, patients were subsequently divided into 2 groups; Group (1) which included 50 patients in whom intracoronary bolus plus infusion of GPI was used during and after PPCI. Group (2) which included 50 patients in whom intracoronary bolus- only GPI was used during PPCI. *Eptifibatide* dose: 180 mcg/kg, 2 boluses were given intracoronary 10 minutes apart then continuous infusion 2 mcg/kg/min IV after PPCI for 24 hours to group (1) only. *Tirofiban* dose: 25 mcg/kg IC bolus to all patients then continuous infusion 0.15mcg/kg/min IV after PPCI for 24 hours to group (1) only.

Study end points

- a) Primary end point: Composite end point of in-hospital mortality, reinfarction, bleeding (according to TIMI classification) and stroke.
- b) Secondary end point: 30 days all cause mortality and reinfarction.

Statistical analysis

Data are presented as mean±SD for continuous data and as number (%) for categorical data. Between groups analysis was done using student t-test for continuous data and Chi-square test (or Fischer exact test) for qualitative data. Level of evidence was detected to be significant at P value <0.05. Data were collected and analyzed by SPSS (version 17, USA, IL).

Results

Study population

The mean age was 50.52 ± 8.38 years (52.1 ± 8.37 years versus 48.94 ± 8.38 years in group 1,2 respectively, $P=0.062$), 75% were males (72% versus 78% in group 1,2 respectively, $P=0.488$), 37% had diabetes (44% versus 30% in group 1,2 respectively $P=0.147$), 76% had hypertension (74 % versus 78% in group 1,2 respectively $P=0.64$), 31 % had dyslipidemia (38% versus 24% in group 1,2 respectively $P=0.13$), 59 % were smokers (56% versus 62% in group 1,2 respectively $P=0.542$), 18% had positive family history of CAD (20% versus 16% in group 1,2 respectively $P=0.602$), 9 % had prior history of MI (18% versus 0 % in group 1,2 respectively $P=0.002$), 10% had history of prior PCI (18% versus 2% in group 1, 2 respectively $P =0.008$) ,no history of prior heart failure in both group. Between groups comparison showed statistical significant difference between groups regarding previous MI and previous PCI while no statistically significant difference was found between them regarding other baseline characteristics (Table 1).

Table (1): Baseline characteristics of study population

Variable	All patients n = 100	Group 1 Bolus and maintenance no = 50	Group 2 Bolus only n = 50	P value
Age ,years				
Mean \pm SD	50.52 \pm 8.38	52.1 \pm 8.37	48.94 \pm 8.38	0.062
Male Sex, n(%)	75 (75%)	36 (72%)	39 (78%)	0.488
Family history of CAD	18 (18%)	10 (20%)	8 (16%)	0.602
DM	37 (37%)	22 (44%)	15 (30%)	0.147
Hypertension	76 (76%)	37 (74%)	39 (78%)	0.64
Smoking	59 (59%)	28 (56%)	31 (62%)	0.542
Dyslipidemia	31 (31%)	19 (38%)	12 (24%)	0.13
Prior MI	9 (9%)	9 (18%)	0 (0%)	0.002
Prior PCI	10 (10%)	9 (18%)	1 (2%)	0.008
Prior CABG	0 (0%)	0 (0%)	0 (0%)	----

CAD: Coronary artery diseases

PCI: Percutaneous coronary intervention

DM: Diabetes Mellitus

CABG: Coronary artery bypass grafting

Clinical presentation on admission

Chest pain was the main symptoms on admission in both groups (100%), 29% of patients were presented with dyspnea (30% in group 1 versus 28% in group 2, P=0.826), 15% of patients were presented with palpitations (8 % in group 1 versus 22 % in group 2, P =0.05).

Target infarction detected by ECG

56% had anterior infarction (54% versus 58% in group 1,2 respectively, $P = 0.687$), inferior infarction was reported in 27% of patients (30% versus 24% in group 1,2 respectively, $P = 0.499$), 2 % of patients had lateral infarction (4 % versus 0% in group 1,2 respectively $P = 0.153$), 10 % of patients had antero lateral infarction (10% versus 10 % in group 1,2 respectively, $P = 1.00$), infero lateral infarction was reported in 2% of both groups (0% versus 4% in group 1,2 respectively $P = 0.153$), antero septal infarction was reported in 3% of patients (2% versus 4% in group 1,2 respectively, $P = 0.558$).

Time from onset of symptoms to admission

The mean time was 6.59 ± 1.84 hours in all patients (6.55 ± 1.78 hours in group 1, versus 6.63 ± 1.91 hours in group 2, $P = 0.838$), 60 % of all patients were presented less than 6 hours (58 % versus 62 % in group 1, 2 respectively, $P = 0.683$), 40 % were admitted between 6-12 hours from onset of symptoms (42 % in group 1 versus 38% in group 2, $P = 0.683$) (Figure 1).

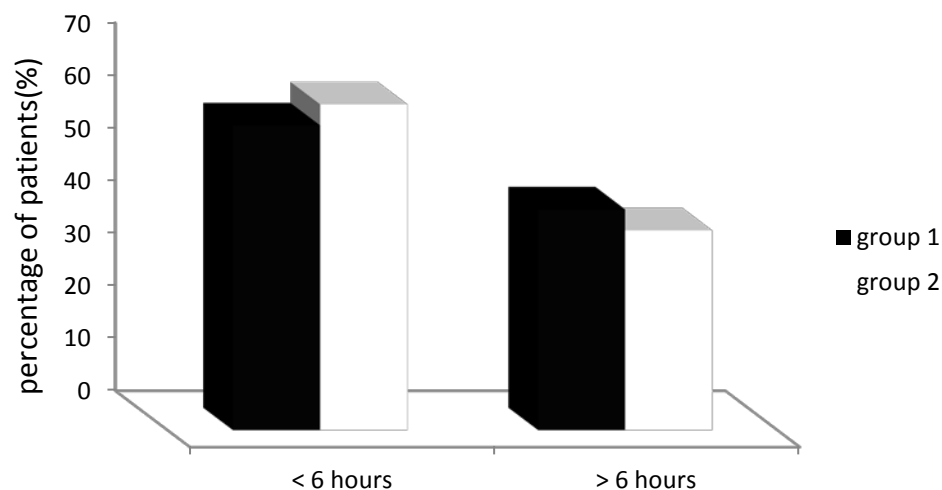


Figure 1. Time from onset of symptoms to hospital admission.

Door to balloon time

The mean time was 81.46 ± 14.39 minutes in all patients (79.71 ± 15.42 minutes in group 1, versus 83.21 ± 13.19 minutes in group 2, $p = 0.225$).

Coronary angiography before PPCI

Number of diseased vessel were single vessel in 48% of patients ,two vessels in 35% of patients and three vessel in 17% of patients. The culprit artery was LAD in 70% of all patients (72% versus 68 % in group 1, 2 respectively, $P = 0.663$), RCA in 25% (26% versus 24% in group 1,2 respectively, $P = 0.817$), while LCX in 2% of both groups (2% in each group). Diagonals were the culprit vessel in 3% of both groups (0% versus 6% in group 1,2 respectively, $P = 0.079$). TIMI flow pre PCI was 0 in 67% of all patients (80% versus 54% in group 1, 2 respectively $P = 0.019$), while TIMI flow I was present in 22% of all patients (12% versus 32% in group 1,2 respectively $P = 0.019$), TIMI flow II was present in 11% of all patients (8% versus 14% in group 1,2 respectively $P = 0.019$).

Procedural data

All patients received 10000 units of UFH pre PCI, femoral approach was done in all patients using 6 French sheath, XB 3.5 guiding catheter was used in 53% of all patients and JR was used in 25% of all patients, while in 22% of patients JL were used ($p = 0.007$), floppy wire was used in 91% of all patients, while covered wire in 9% of patients ($p = 0.212$), predilatation was done in 53% of all patients ($p = 0.16$), aspiration devices were used in 20% of all patients, $P = 1.0$. The stent number was one in 95% of all patients (96% versus 94% in group 1,2 respectively), while two stents in 5% of all patients (4% versus 6% in group 1,2 respectively), the mean stent length was 24.76mm (25.60 ± 5.58 mm versus 23.92 ± 6.23 mm in group 1 and group 2 respectively, $P = 0.159$), the mean stent diameter was 3.07 ± 0.33 mm (3.08 ± 0.30 mm versus 3.07 ± 0.36 mm in group 1,2 respectively, $P = 0.822$). TIMI flow post PPCI was III in

87% of all patients (86% versus 88% in group 1,2 respectively), TIMI flow II was 10% of all patients (12% versus 8% in group 1,2 respectively), while TIMI flow I was 3% of all patients (2% versus 4% in group 1,2 respectively), $P=0.74$. The mean procedural time was 47.28 ± 6.30 minutes in all patients (47.78 ± 6.48 min versus 46.78 ± 6.14 min in group 1,2 respectively, $P=0.430$), no reflow was reported in 3% of all patients (4% versus 2% of group 1,2 respectively, $P=0.5$), dissection occurred in 3% of all patients (2% versus 4% of group 1,2 respectively, $P=0.5$)

In hospital outcome

Primary end point was reported in 54% of patients in group 1 Vs 38% in group 2 ($p=0.1$). Recurrence of chest pain was reported in 7% of all patients (4% versus 10% of group 1,2 respectively, $P=0.2$), minor bleeding occurred in 12% of all patients (18% versus 6% in group 1,2 respectively, $P=0.06$), major bleeding occurred in 1% of all patients (2% versus 0% in group 1,2 respectively, $P=0.3$). Contrast induced nephropathy was evident in 5% in all patients (8% versus 2% of group 1,2 respectively, $P=0.169$), stent thrombosis occurred in 1% of all patients (1% of group 2 but not in group 1, $P=0.3$), heart failure occurred in 13% of all patients (14% versus 12% in group 1,2 respectively, $P=0.7$), also ventricular arrhythmia was reported in 3% of all patients (2% versus 4% in group 1,2 respectively, $P=0.5$), death occurred in 2 patients in group 1 but not in group 2, ($P=0.1$). No reported cases of cardiogenic shock and reinfarction in either group.

30 days outcome

Combined end point of adverse cardiovascular events (mortality and reinfarction) was reported in 8% of all patients (10% versus 6% in group 1,2 respectively, $P=0.4$). All cause mortality occurred in 5% of patients (8% versus 2% in group 1,2 respectively, $P=0.1$). Reinfarction was reported in 3% of patients (2% versus 4% in group 1,2 respectively, $P=0.5$).

Discussion

Glycoprotein IIb/IIIa inhibitors (GPI) are beneficial in reducing ischemic complications in patients undergoing PCI⁽²⁾. Several randomized trials showed a reduction in MACE of death, MI, and urgent revascularization by 35% to 50% when compared with placebo in a wide variety of PCI settings⁽³⁾. Traditionally, GPI are administered as intravenous bolus followed by a prolonged 12 to 18 hours infusion⁽²⁾. However, this bolus followed by infusion strategy, may be associated with increased vascular/bleeding complications⁽⁴⁾. This study evaluated the short term outcome of bolus only GPI versus bolus followed by infusion of GPI during PPCI. We reported that GPI bolus-only reduces bleeding complications with similar MACE. In the present study there was no significant difference between groups in the culprit artery nor time from symptom onset. Our study findings are in agreement with prior trials^(10,11,12,13). In our study, in-hospital major bleeding occurred in 2% in group (1) versus 0% in group (2) (p=0.3). while in-hospital minor bleeding occurred in 18% of patients in group (1) versus 6% in group (2) (p=0.06). We observed that there is reduction in bleeding complications with bolus-only dosing of GPI but not reaching statically significant value. Kini et al., 2008⁽¹⁰⁾ reported 1.9% versus 3.8% bleeding complications with bolus only versus bolus plus maintenance. Bertrand et al. 2006⁽¹³⁾, reported that the bolus-only strategy was non-inferior with respect to decrease major bleeding In Fung et al., 2009⁽¹²⁾ in hospital major bleeding was reported in a total of 16 patients, 3 in the <2 h infusion group and 13 in the 18 h group (1.0% vs. 4.2%, p= 0.02). Among the 624 patients randomized, 29 patients had early termination of the eptifibatide placebo infusions due to clinically overt bleeding complications (20 in the <2-h group and 19 in the 18 h group); and transfusion of blood products was given to 2 patients because of access site bleeding (both in the <2 h group). In the present work, although there are no significant different between both groups as regard most parameters of the in hospital outcome, there is a trend toward increased incidence of

minor bleeding (18% vs. 6%), major bleeding (2% vs. 0%), renal impairment(8% vs 2%), stroke (2% vs. 0%) , death (2% vs. 0%) and total primary end point(54% vs 38%) in group (1). However, there are marginal differences as regard stent thrombosis (0% vs. 2%), recurrent chest pain (4% vs. 10%), ventricular arrhythmia (2% vs. 4%) and heart failure (14% vs. 12%) in group 1 and 2 respectively. So the results of the present work revealed a trend toward reduction in bleeding complications, renal impairment, stroke& death in the expense of marginal increase in stent thrombosis, recurrent chest pain and ventricular arrhythmia.

As regard the 30 days outcome, the current study shows a higher incidence of combined end point of adverse cardiovascular events (Death and re-infarction) in group (1) compared to group (2), however the differences did not reach statistical significance. Our study findings are in agreement with Kini et al.,2008 ⁽¹⁰⁾ regarding short term clinical outcome, who stated that ischemic complications including periprocedural, acute or sub acute stent thrombosis, and MACE at 30 days were reported in 99% in the GPI bolus only and in 99% in the GPI bolus plus infusion. Furthermore, death and MI at 1 year was evident in 90% in the GPI bolus-only and in 91% in the GPI bolus plus infusion. Our study findings are also in agreement with the EASY trial by Bertrand et al., 2006 ⁽¹³⁾, in which the bolus-only strategy was non-inferior with respect to the 30-day occurrence of death or adverse ischemic events. Fung et al., 2009 ⁽¹²⁾ reported similar results as regard the 30 day incidence of myocardial infarction, death, and target vessel revascularization.

Conclusion

The results of the current study suggest that bolus-only GPI is not inferior to bolus followed by 24- hours GPI infusion as regard short term outcome with a trend for fewer mortality and bleeding complication rate.

Recommendations

A large prospective randomized, multi-centre trial with a longer follow up period is needed to confirm our observation.

Study limitations:

- The small sample size.
- Single center study.
- Lack of randomization.
- Short follow up.
- No platelet aggregation studies were done to support the clinical equivalence noted between 2 groups.

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