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Clinical paper

Safety of glycoprotein IIb/IIIa inhibitors in patients under therapeutic hypothermia admitted for an acute coronary syndrome☆

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ABSTRACT

Background: Mild therapeutic hypothermia (MTH) is associated with an increased risk of both thrombotic and bleeding events. Although little is known about the use of Glycoprotein IIb-IIIa inhibitors (GPi) in this setting, the early action and the intravenous administration of these agents in patients who cannot swallow might potentially translate into clinical benefits in patients with acute coronary syndromes (ACS).

Aims: To assess the incidence of bleeding/thrombotic events in patients with ACS under MTH after an Out-of-hospital cardiac arrest (OHCA) who received GPi or not.

Methods and Results: From January 2010 to September 2015, 110 patients were treated with MTH after an OHCA. Among them, 88 (80%) had an ACS and 71 patients (80.6%) underwent percutaneous coronary intervention (PCI). In 17 (24%) GPi were administered in the cath-lab. During hospitalization, 11.7% in the GPi and 9.25%in the non GPi group presented thrombotic events (stent thrombosis, deep vein thrombosis, pulmonary embolism) without significant differences between groups ($p = 0.762$). The incidence of any bleeding (64.7% vs. 14.8%; $p < 0.0001$), and major bleeding (41.1% vs. 3.7; $p < 0.0001$) was significantly higher in patients receiving GPi. Finally, in-hospital mortality did not differ between groups (24% vs. 35, 2%; $p = 0.385$).

Conclusions: In this study, the use of GPi in patients with ACS undergoing PCI under MTH was associated with an increased bleeding risk without reduction of thrombotic events. According to these results, the use of GPi should be carefully considered in this setting.

Introduction

Acute coronary syndromes (ACS) are the leading cause of cardiac arrest.[1,2] European guidelines recommend urgent coronary angiography with a view to primary percutaneous coronary intervention (PCI) in survivors of Out-of-hospital cardiac arrest (OHCA).[2,3] Mild therapeutic hypothermia (MTH) has been proposed as a valid option to preserve neurological status in these patients.[2] However, post resuscitation syndrome and MTH may produce alterations in haemostasis and coagulopathy.[4] Hypothermia below 33° affects the synthesis and kinetics of clotting enzymes, thrombin generation, and plasminogen activator inhibitors and is related to platelet dysfunction, and this may be associated with an increased risk of both thrombotic and bleeding events.[5,6] In this regard, Orban et al. reported an increase in major bleeding in patients in cardiogenic shock treated with primary PCI and MTH compared to those without MTH.[7] Similarly, Gouffran et al. observed a major bleeding rate of 25.7% according to the Bleeding Academic Research Consortium (BARC)[8] in a cohort of 101 OHCA survivors treated with primary PCI and MTH.[9] In contrast, other published series of patients undergoing PCI and MHT have reported an increased risk of not only bleeding but also thrombotic events including stent thrombosis. Among other factors, the increased platelet activity and the

Abbreviations: ACS, Acute coronary syndrome; BARC, Bleeding Academic Research Consortium; DVT, Deep vein thrombosis; GPi, Glycoprotein IIb-IIIa inhibitors; ICU, Intensive Cardiac Unit; LVEF, Left ventricle ejection fraction; MTH, Mild therapeutic hypothermia; OHCA, Out-of-hospital cardiac arrest; PCI, Percutaneous coronary intervention; PE, Pulmonary embolism; ST, Stent thrombosis.

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insufficient platelet inhibition by P2Y12 inhibitors seem to be the major reasons for these events.[5,8,12,13]

The use of Glycoprotein IIb-IIIa inhibitors (GPi) is considered for bailout situations or thrombotic complications in patients with ACS.[10] Although the use of GPi has been related to increased risk of bleeding, GPi have shown clinical benefits in patients with high thrombotic burden.[11] Since MHT seems to be a pro-thrombotic setting, the early action of GPi and the intravenous administration in patients who cannot swallow might potentially translate into clinical benefits in patients with acute coronary syndromes (ACS) after OHCA.[14] Thus, the aim of the study was to assess the clinical benefit of GPi in patients with ACS undergoing PCI under MTH by evaluating the incidence of bleeding/thrombotic events based on the use of GPi or not.

Methods

Patients

This was a single centre and observational study. We screened consecutive patients admitted to our Hospital between January 2010 and September 2015 with ACS and OHCA undergoing PCI under MTH. Exclusion criteria included the use of coumadin derivates, previous use of fibrinolytic agents and patients who died before the index procedure.

Procedural characteristics

All surviving OHCA patients with high suspicion of ACS were admitted to the cardiac catheterization laboratory regardless of the clinical and ECG findings. Patients were treated with aspirin and heparin prior to hospital admission or during the procedure. Primary PCI was attempted if there was an acute coronary atherothrombotic lesion. The use of GPi and manual thrombus aspiration were left to the operator preference but generally used in cases of large thrombotic burden. The arterial access (radial or femoral) was also decided by the operator based on the quality of the artery and the clinical status of the patient. After PCI all patients were transferred to the Intensive Cardiac Unit (ICU).

A loading dose of P2Y12 inhibitors (clopidogrel 600 mg, prasugrel 10 mg or ticagrelor 180 mg) was crushed, dissolved and administered by nasogastric tubing right after PCI. The loading dose was followed by maintenance dose (clopidogrel 75 per day, prasugrel 10 mg per day, ticagrelor 90 mg bid).

Hypothermia therapy

All patients received MTH according to the local ICU protocol. MHT was started in the emergency area by the administration of 4 °C saline, 30 ml/kg (maximum: 2 l) infused in 30 min. Infusion was stopped if the temperature was 33.5 °C. In the intensive care unit, patients received standard treatment that included mechanical ventilation and correction of cardiovascular instability. All patients were sedated with an infusion of midazolam and morphine at doses that were adjusted for the management of mechanical ventilation. Neuromuscular relaxation was achieved with cisatracurium infusion to avoid muscular tremor. A urinary catheter with temperature sensor (Foley catheter, Rüsch sensor series 400 [silicon], Curity, Tyco, Athione, Ireland) was implanted. The extracorporeal MHT system (Medivance Arctic Sun System, Louisville, Colorado) was used to control temperature. All patients reached 33 °C fewer than 8 h from cardiac arrest, and this temperature was maintained for 24 h. Warming took place gradually in 24–30 h, with a rate of 0.10–0.15 °C/h.

Data analysis

The baseline and procedural data of patients were systematically collected in a dedicated database. The primary endpoint was the occurrence of thrombotic events including definite and probable stent thrombosis (ST),[15] deep vein thrombosis (DVT), and pulmonary embolism (PE) during hospitalization, as well as the incidence of bleeding events according to the BARC criteria.[8]

Thrombus grade was classified according to TIMI criteria[16] with later reclassification, if possible, of total occlusions after initial flow restoration in accordance with Sianos et al.[17]: Grade 0, no angiographic characteristics of thrombus present; Grade 1, possible thrombus present, with such angiography characteristics as reduced contrast density, haziness, irregular lesion contour, or a smooth convex meniscus at the site of total occlusion suggestive, but not diagnostic, of thrombus; Grade 2, definite thrombus with largest dimension ≤½ the vessel diameter; Grade 3, definite thrombus, with largest linear dimension >½ but <twice vessel diameter; Grade 4, definite thrombus, with the largest dimension ≥2 vessel diameters; Grade 5, total occlusion, unable to assess thrombus burden due to total vessel occlusion. In this study the highest thrombus grades (4 and 5) were grouped into a variable for study.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and non-normally distributed variables were expressed as median [inter-quartile range]. Categorical variables were expressed as count and percentage. Baseline characteristics between groups were compared using *t* test for continuous variables and chi-square test for categorical variables. Results were considered statistically significant at a *p*-value <0.05. Statistical analyses were carried out using SPSS package v16.0 (Chicago, IL, USA).

Results

From January 2010 to September 2015, 110 patients were treated with MTH after an OHCA. Among them, 88 (80%) had an ACS of which 71 patients (80.6%) were treated with primary PCI, 17 (24%) with GPi (GPi group) and 54 (76%) without GPi (non-GPi group).

Baseline characteristics are presented in Table 1. No significant differences were observed but a lower mean age in the GPi group. Similarly, features related to clinical presentation did not differ between groups (Table 2). Of note, all patients in the GPi and 83.3% in the non-GPi group presented cardiac arrest caused by STEMI. Procedural data revealed no significant differences in the use of new P2Y12 inhibitors, but a higher thrombotic burden and higher use of manual thromboaspiration in the GPi group (Table 3). However,

Table 1
Characteristics of the patients at baseline.

	GPi (*n*: 17)	Non GPi (*n*: 54)	*p*: Value
Age, years, mean ± SD	52.76 ± 12.3	60.1 ± 11.5	0.027
Male, no. (%)	15 (88.2)	45 (83.3)	0.626
Smoking, no. (%)	11 (64.7)	25 (46.2)	0.260
Hypertension, no. (%)	4 (23.5)	24 (44.4)	0.237
Diabetes mellitus, no. (%)	2 (11.7)	8 (14.8)	0.804
Hypercholesterolemia, no. (%)	7 (41.1)	21 (38.9)	0.722
Family history of coronary artery disease, no. (%)	3 (17.6)	5 (9.2)	0.444
Previous myocardial infarction, no. (%)	1 (5.9)	12 (22.2)	0.205
Renal failure, no. (%)	0 (0)	4 (7.4)	0.429