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Clinical paper

Out-of-hospital cardiac arrest and stent thrombosis: Ticagrelor versus clopidogrel in patients with primary percutaneous coronary intervention under mild therapeutic hypothermia☆

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ABSTRACT

Background: Out-of-Hospital Cardiac Arrest (OHCA) and mild therapeutic hypothermia (MTH) have been linked to increased risk of Stent Thrombosis (ST) in comatose survivors who undergo percutaneous coronary intervention (PCI). In this sense, there is no formal recommendation about which antiplatelet regimen should be used in patients with acute coronary syndromes (ACS) after OHCA.
Aims: To compare the incidence of probable/definite ST and bleeding events between ticagrelor and clopidogrel, in patients with ACS under MTH after an OHCA.
Methods and results: From January 2010 to August 2016, 144 patients underwent MTH after an OHCA. Overall, 114 had an ACS (79%) and 98 (67,3%) were treated with primary PCI and stent implantation. Among them, 61 (62,2%) were treated with clopidogrel, and 32 (32,6%) with ticagrelor. During hospitalization, the incidence of probable or definite ST was significantly higher in patients receiving clopidogrel compared to ticagrelor (11,4% vs. 0%; p: 0.04), and no significant differences in any (28,6% vs. 25%; p: 0.645) or major bleeding (BARC 3 or 5) (11,4% vs. 12,5%; p: 0.685) were found. Hospital mortality did not differ between groups (26,2% vs. 25%; p: 0.862).
Conclusions: In this study, as compared to clopidogrel, ticagrelor was associated with a lower rate of ST, without differences in haemorrhagic events in patients with OHCA for an ACS under MTH. Similarly to other settings, ticagrelor might be a valid alternative to clopidogrel in these patients.

Introduction

Acute coronary syndromes (ACS) are the commonest cause of malignant arrhythmias leading to sudden cardiac death.[1] Mild therapeutic hypothermia (MTH) and emergent coronary angiography with primary percutaneous coronary intervention (PCI) improves outcomes in the setting of Out-of-Hospital Cardiac Arrest (OHCA) after a coronary event.[2,3] MTH has been proposed to preserve neurological status in these patients.[4]

MTH has been associated with haemostasis and coagulopathy disorders.[5,6] The relationship between a higher risk of stent thrombosis (ST) and OHCA is very controversial. Whereas several studies have reported a higher risk of stent thrombosis (ST) after primary PCI in OHCA patients,[7–12] some other studies did not find this association.[13,14]

A recent study suggested that just the fact of having suffered an OHCA by itself increases the risk of ST regardless the use of MTH.[12]

Alterations in platelet reactivity and pharmacokinetics of antiplatelet agents with MTH may pre-dispose to ST in these patients.[9–11]

Dual antiplatelet therapy (DAPT) with aspirin and P2Y12 inhibitor are the standard of care for patients after PCI.[15] Accord-

Abbreviations: ACS, acute coronary syndrome; BARC, bleeding academic research consortium; BMS, bare metal stent; DAPT, dual antiplatelet therapy; DES, drug eluting stent; GP IIb-IIIa, glycoprotein IIb-IIIa receptors; ICU, intensive cardiac unit; LVEF, left ventricle ejection fraction; MTH, mild therapeutic hypothermia; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; ST, stent thrombosis.

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ingly, DAPT has been integrated into management of patients after OHCA who undergo PCI and subsequently are treated with MTH. Nonetheless there is no formal recommendations about which antiplatelet regimen should be used in patients with ACS and OHCA.[1]

In the PLATelet inhibition and patient outcomes (PLATO) trial, ticagrelor was associated with a significant reduction of cardiovascular events, cardiovascular mortality, all cause mortality and ST in patients with ACS compared to clopidogrel,[16] In this regard, Tilemann et al. reported that the administration of crushed ticagrelor via nasogastric tube reliably inhibited platelet function regardless of the presence of hypothermia in ACS patients,[17] and other studies confirm these findings.[18–20]

Previous reports showing increased ST in OHCA patients with MTH did not focus in antiplatelet treatment until although surprisingly, Gouffran et al. observed an increase of ST in patients treated with new P2Y12 inhibitors receptors (ticagrelor or prasugrel) compared to clopidogrel in a cohort of 101 OHCAs treated with PCI and MTH.[12] Thus, the aim of the study was to compare the incidence of ST and bleedings events between ticagrelor or clopidogrel in patients with ACS undergoing PCI after OHCA under MTH.

Methods

Patients

This was a single centre observational study. We retrospectively screened consecutive patients admitted to our Hospital between January 2010 and August 2016 with ACS and OHCA undergoing primary PCI under MTH. Exclusion criteria included patients with ACS without stent implantation, and patients who died before the index procedure. Although patients who received prasugrel were included in the main cohort, the small number of subjects in this group precluded any specific comparison with ticagrelor or clopidogrel. The study was approved by Ethics Committee of our centre (approval reference number 2013/8596) and complies with principles laid down in the Declaration of Helsinki.

Procedural characteristics

All surviving OHCA patients admitted to our centre without an evident extra cardiac cause were admitted immediately to the cardiac catheterization laboratory regardless of the clinical and ECG findings. If there was a high suspicion of ACS defined by ECG changes, initial shockable rhythm or previous chest pain, antithrombotic treatment with aspirin and heparin was initiated by emergency team prior to admission. Primary PCI was attempted if there was an acute coronary atherothrombotic lesion. The use of glycoprotein IIb-IIIa receptors inhibitors (GPI IIb-IIIa) and manual thrombus aspiration were left to the operator preference. The length, diameter and type of stent Drug Eluting Stent (DES) or Bare Metal Stent (BMS), were also decided by the operator. After PCI all patients were transferred to the Intensive Cardiac Unit (ICU).

In order to reduce delays, most of the patients arrived without nasogastric tubing at the cardiac catheterization laboratory. Nasogastric tubing was therefore placed in the cath lab just after PCI, so the loading dose of P2Y12 inhibitors was crushed, dissolved and administered right after the PCI. Unfortunately, there was no accurate estimation of the time delay between PCI and P2Y12 inhibitors administration. P2Y12 inhibitors were however always administered within the 30 min after PCI and prior to the ICU transfer. Although small, this variable delay in drug administration may have contribute to the final results, as ticagrelor has a faster mechanism of action compared to clopidogrel.

The loading dose was followed by maintenance dose (clopidogrel 75 per day, prasugrel 10 mg per day, ticagrelor 90 mg bid.)

All patients received MTH according to the local ICU protocol. 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. This protocol has been comprehensively described somewhere else.[7] In the ICU, patients received standard treatment that included mechanical ventilation and correction of cardiovascular instability.

Data analysis

The baseline and procedural data of patients were systematically collected in a dedicated database. The primary endpoint was the occurrence of definite and probable stent thrombosis (ST),[21] during hospitalization according to the Academic Research Consortium definitions, as well as the incidence of bleeding events according to the BARC criteria.[22]

A routine angiography was not compulsory after baseline PCI and was only performed in case of a clinical event, ECG or echocardiography changes or severe hemodynamic instability.

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 v20.0 (Chicago, IL, USA).

Results

From January 2010 to August 2016, 144 patients were treated with MTH after an OHCA. Overall, 114 had an ACS (79%) and 98 (67,3%) underwent with primary PCI with stent implantation. Among them, 61 (62,2%) were treated with clopidogrel, (clopidogrel group), 32 (32,6%) with ticagrelor (ticagrelor group) and 5 patients were treated (5,1%) with prasugrel.

As shown in Table 1, baseline characteristics were similar among groups. Of note, most of the patients presented cardiac arrest secondary to STEMI. Post-resuscitation shock was similar in both groups (65.5% in the clopidogrel group vs. 71.8% in the ticagrelor group; p = 0.67). As shown in Table 2, procedural data revealed no significant differences in the use of GP IIb-IIIa inhibitors or thromboaspiration, but a significant higher use of DES in the ticagrelor group.

Clinical outcomes

During hospitalization, 7 (7.1%) patients presented definite or probable ST, 7 (11,4%) in the clopidogrel group and none (0%) in the ticagrelor group (p:0,04). None of five patients with prasugrel presented ST (Table 3). Stent thrombosis was classified as acute in 2 patients and sub acute in the other 5 patients. Two patients with DES and 5 with BMS presented definite ST.

DES were implanted in 33 patients (16 in the clopidogrel and 17 in the ticagrelor group). Only 2 patients in the clopidogrel group (12.5%) presented ST and there were no significant differences among groups (12.5% vs. 0%, p = 0.13). An individual and more comprehensive description of ST is provided in Table 4.

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