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The impact of mild therapeutic hypothermia on platelet reactivity in comatose survivors of cardiac arrest with acute myocardial infarction treated with ticagrelor

Julia M. Umińska et al., The impact of mild therapeutic hypothermia on platelet reactivity

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Abstract

Background: The aim of the study was to assess the antiplatelet effect of ticagrelor in patients with myocardial infarction (MI) after out-of-hospital cardiac arrest (OHCA) treated with percutaneous coronary intervention (PCI) and mild therapeutic hypothermia (MTH) vs. MI patients without OHCA treated with PCI.

Methods: The study was designed and performed as a phase IV, single-center, investigator-initiated, prospective, observational study assessing the early pharmacodynamic effect (within first 24 h) of a ticagrelor loading dose (180 mg) in both groups of patients (MTH group vs. MI group). For assessment of ticagrelor pharmacodynamics Multiple Electrode Aggregometry (MEA) was applied.

Results: Compared with the MTH group, platelet inhibition was persistently stronger in the MI group over the entire observation period (up to 24 h), with the highest difference at 4 hours after loading with ticagrelor (25.8 ± 26.4 vs. 75.8 ± 40.9 U, $p = 0.002$). As a consequence, there was a higher prevalence of high platelet reactivity in the MTH group, with the most explicit difference at 6 hours after the loading dose of ticagrelor (78% vs. 7%, $p < 0.001$).

Conclusions: In comparison with patients treated with primary PCI for uncomplicated MI, the antiplatelet effect of ticagrelor in patients with MI complicated with OHCA, undergoing MTH and primary PCI, is attenuated and delayed.

Key words: cardiac arrest, myocardial infarction, hypothermia, ticagrelor, pharmacodynamic, platelets

Introduction

Out-of-hospital cardiac arrest (OHCA) is a frequent complication of acute myocardial infarction (MI) [1–7]. OHCA survivors presenting symptoms of acute MI require primary percutaneous coronary intervention (pPCI) with concomitant dual antiplatelet treatment (DAPT) including acetylsalicylic acid (ASA) and a P2Y₁₂ receptor inhibitor [8–10]. It has been shown that the antiplatelet effect of ticagrelor is diminished in patients with ST-elevation MI in the setting of OHCA and may be further deteriorated due to mild therapeutic hypothermia (MTH) [8–12].

Thus, designed herein [13], and performed is a prospective observational study comparing the antiplatelet effect of ticagrelor in MI patients after OHCA treated with pPCI and MTH vs. MI patients without OHCA treated with PCI.

Methods

The study was designed and performed as a phase IV, single-center, investigator-initiated, prospective, observational study assessing the impact of OHCA treated with MTH on early pharmacodynamic effect (within first 24 h) of ticagrelor loading dose (180 mg) in MI patients undergoing pPCI. The loading dose of ticagrelor was administered in the cath-lab, right before percutaneous coronary intervention and hypothermia induction. Therefore, platelet reactivity could be compared in MI patients after OHCA treated with pPCI and MTH vs. MI patients without OHCA treated with PCI. The inclusion as well as exclusion criteria for both groups have been previously published [13]. For objective reasons, no informed consent could be obtained from patients treated with MTH due to OHCA, however no additional blood sampling was required outside the protocol of MTH monitoring. MTH was defined as body core temperature below 34°C, with a target temperature of 33°C. In order to reach the target temperature and maintain it over the subsequent 24 hours intravascular cooling supported by cold saline (4°C) infusion and external cooling at the induction phase of MTH was used.

Blood samples were drawn at predefined time points: before administration of a 180-mg loading dose of ticagrelor, thereafter at: 30 minutes, and at 1, 2, 4, 6, 12, and 24 hours. For assessment of ticagrelor pharmacodynamics Multiple Electrode Aggregometry (MEA) was applied. The measurements were performed using a semi-automatic Multiplate analyzer (Roche Diagnostics International Ltd., Rotkreuz, Switzerland). The results of platelet reactivity assessment were expressed as ADP-induced platelet aggregation units [U]. The prevalence of high and low platelet reactivity (HPR and LPR) was assessed at each time-point. Cut-off points for MEA had been previously defined as HPR > 46 U and LPR < 19 U [13].

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Ethics Committee of The Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz (approval number KB 339/2015). This is a sub-study of the Mild Therapeutic Hypothermia for Patients With Acute Coronary Syndrome and Cardiac Arrest Treated With PCI (UNICORN) study (ClinicalTrials.gov Identifier: NCT02611934) [5]. The project was supported by a Diamond Grant from the Ministry of Science and Higher Education of the Republic of Poland from research funds for the years 2015–2018.

Statistics description

All calculations were performed using Statistica 13.0 software (StatSoft, Tulsa, OK, USA). Continuous variables are presented as means \pm standard deviation and median with quartiles. For categorical variables, counts with percentages have been used. Due to non-normal data distribution (as verified with the Shapiro-Wilk test), comparisons between both groups at each measurement point were performed with the Mann-Whitney test. For comparison of categorical variables, the χ^2 test or the Fisher exact test was applied as appropriate. P-value ≤ 0.05 was considered significant.

Results

The study group (MTH group) initially comprised 13 MI patients after OHCA, treated with MTH and pPCI. The control group (MI group) consisted of 30 MI patients without OHCA treated with pPCI. Among the 13 patients eligible for the study group, 2 died during first hours after admission, therefore we finally enrolled and analyzed 11 OHCA patients treated with pPCI, MTH, and ticagrelor. All of them had ventricular fibrillation as the initial rhythm during cardiac arrest (Table 1).

A comparison of platelet reactivity in both groups showed a significant discrepancy starting from the first hour after administration of the loading dose of ticagrelor (Fig. 1). In comparison with the MTH group, platelet inhibition was persistently stronger in the MI group over the entire observation period (up to 24 h), with the highest difference at 4 hours after loading with ticagrelor (25.8 ± 26.4 vs. 75.8 ± 40.9 U, $p = 0.002$). As a consequence, there was a higher prevalence of HPR in the MTH group as compared with the MI group, with the most explicit difference at 6 hours after the loading dose of ticagrelor (78% vs. 7%, $p < 0.001$) (Fig. 2). Twenty-four hours after loading with ticagrelor, all patients in both groups were found to have effective platelet inhibition, however a stronger effect persisted in the MI group (15.9 ± 10.4 vs. 28.7 ± 13.3 U, $p = 0.026$; Fig. 1).

Discussion

The main finding of the present study is a significant attenuation and delay of platelet inhibition within 24 hours after administration of a ticagrelor loading dose in patients undergoing MTH and pPCI due to OHCA in the course of MI, as compared with patients treated with pPCI for uncomplicated MI. This observation remains in line with our previous publication reporting

the impact of MTH on bioavailability of ticagrelor [14]. Lower total exposure, lower maximal plasma concentration and delayed maximal plasma concentration of the drug in patients undergoing MTH in comparison with patients with uncomplicated MI, advocates impaired gastrointestinal absorption of ticagrelor in critically ill patients undergoing therapeutic hypothermia. Different rates of active metabolite (AR-C124910XX) formation between the groups were compared in the study, suggesting potential diversity in drug metabolism and/or elimination [14]. These observations may account for the increased rate of stent thrombosis reported in some studies in resuscitated MI patients treated with MTH and pPCI to be caused by insufficient inhibition of P2Y₁₂ platelet receptors [15–18].

Tilemann et al. [19] evaluated the efficacy of ticagrelor 24 hours after loading dose administration in MI patients with and without MTH following OHCA. A shift towards higher platelet reactivity at lower body temperature was observed in hypothermic patients, although the difference did not reach statistical significance. The authors concluded that ticagrelor is effective in MI patients after OHCA, however the evaluation of platelet reactivity was only performed after 24 hours, while according to the present data, the highest differences occurred between 2 and 12 hours after the administration of ticagrelor loading dose. Moreover, in the same study, a strong inverse correlation between platelet reactivity on ticagrelor and the temperature of blood samples was found, suggesting weaker platelet inhibition while cooling [19].

In a study assessing platelet function after a loading dose of ticagrelor in two time-points (at 12 to 24 h after reaching 33°C and at 12 to 28 h after reaching normothermia), the rate of patients on DAPT who reached the target VASP PRI < 50% was as low as 50% at the first sampling and rose to 86% at the second assessment, suggesting impaired bioavailability of ticagrelor in critically ill patients during hypothermia [20]. The comparison of these results with respective prevalence of HPR in the present study is difficult due to broad time range of blood sampling (12–24 h) in the study published by Rosencher et al. [20]. A huge difference was noted in the prevalence of HPR in the MTH group between 12 (63%) and 24 (0%) hours. Much higher rates of non-responders (100% and 83%) were reported in MTH patients treated with clopidogrel [21, 22].

Prüller et al. [23] compared the efficacy of DAPT (ASA and loading doses of either 600 mg of clopidogrel, 60 mg of prasugrel or 180 mg of ticagrelor) in resuscitated acute coronary syndrome (ACS) patients treated with MTH. Blood samples for platelet function testing were

taken every following working day for 7 days in the resuscitation group and only once per patient in the control ACS group within the first 3 days after the index event. The weakest and strongest platelet inhibition was observed on clopidogrel and ticagrelor, respectively, however the net effect of all P2Y12 receptor inhibitors was reduced in comparison with hemodynamically stable ACS patients constituting the control group [23].

Ibrahim et al. [15] investigated the influence of MTH in patients after cardiac arrest on the platelet inhibitory effect of clopidogrel, prasugrel, and ticagrelor determined 24 hours after administration of the loading dose. Significantly higher platelet reactivity was found in the hypothermia group as compared with the normothermia group, indicating a worse response to P2Y12 receptor inhibitors in the former group. The impact of hypothermia was strongest with the use of clopidogrel, as opposed to prasugrel and ticagrelor, where it was weaker, but was still present. The proportion of non-responders was 82%, 32%, and 30%, respectively [15].

In a similar study performed by Bednar et al. [24], platelet reactivity was assessed during 3 consecutive days after MTH initiation. Treatment with clopidogrel was ineffective for the whole 3-day monitoring period in 77% of patients. Significantly better results were obtained with prasugrel and ticagrelor, since only 20% and 10% of patients, respectively, had high on-treatment platelet reactivity on day 1 after loading dose administration. The antiplatelet effect of the newer P2Y12 inhibitors further improved during the following 2 days [24].

In two prospective observational studies assessing OHCA patients undergoing MTH, Moudgil et al. [25] and Rosencher et al. [20] evaluated the pharmacodynamic efficacy of clopidogrel vs. ticagrelor. Effective and sustained platelet inhibition was obtained within 4 hours after drug administration in the majority of patients treated with ticagrelor, while no effect on platelet function was found in subjects on clopidogrel up to the end of observation at day 6 and 7, respectively [15, 25].

Steblovnik et al. [26] reported that treatment with ticagrelor, but not with clopidogrel, resulted in significant suppression of platelet reactivity starting 2 hours after the loading dose and persisting over 48 hours in patients after cardiac arrest, undergoing MTH and PCI. High on-treatment platelet reactivity was found in a lower proportion of patients on ticagrelor compared with clopidogrel at 12 and 48 hours: 11% vs. 53% ($p = 0.01$) and 7% vs. 35% ($p = 0.065$), respectively [26].

Recently Tomala et al. [27] showed effective platelet inhibition obtained with ticagrelor at 12–24 and 48–72 hours in comatose OHCA survivors undergoing pPCI and treated with MTH. Also, in this case the comparison with our results is impossible due to broad time range of blood sampling (12–24 hours) applied in the study by Tomala et al. [27].

The specificity of OHCA survivors treated with MTH implies logistic difficulties in platelet function testing, therefore all studies published so far have included low numbers of patients. Nevertheless, the available evidence suggests that ticagrelor and prasugrel should be preferred over clopidogrel in this patient group. Moreover, even these stronger inhibitors of the P2Y₁₂ receptor do not provide an adequate antiplatelet effect within the first hours after loading dose administration. Therefore, cangrelor — an intravenous P2Y₁₂ inhibitor, should be considered as a bridging therapy in the first day of treatment in OHCA survivors treated with MTH [28–35, 38]. There are no conclusive data supporting the preferential choice of antiplatelet therapy depending on the cooling method.

Similar to previously published reports, a low number of OHCA patients treated with MTH and pPCI is the main limitation of the present study. Observations herein provide important evidence which may help elucidate causes of a higher prevalence of stent thrombosis and other thrombotic events in patients undergoing MTH.

Conclusions

The antiplatelet effect of ticagrelor in patients with MI complicated with OHCA, undergoing MTH and pPCI, was attenuated and delayed in comparison to patients treated with pPCI for uncomplicated MI. However, 24 hours after loading with ticagrelor an adequate platelet inhibition was reached in all survivors in both groups.

Conflict of interest: Julia M. Umińska: beneficiary of the "Diamentowy Grant" financed by the Ministry of Science and Higher Education of the Republic of Poland from research funds for the years 2015–2018 (DI2014009144); Jakub Ratajczak: none declared; Krzysztof Pstrągowski: none declared; Katarzyna Buszko: none declared; Klaudiusz Nadolny: none declared; Tomasz Fabiszak: none declared; Klemen Steblovnik: beneficiary of a research grant from AstraZeneca; Marko Noč: beneficiary of a research grant from AstraZeneca; Jacek Kubica: consulting fee from AstraZeneca.

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Table 1. Characteristics of patients enrolled into the study group (MTH) and control group (MI)

		MTH group (n = 11)	MI group (n = 30)	P
	Gender, male	73% (8)	80% (24)	NS
	Age [years]	62.0 ± 11.9	64.4 ± 10.3	NS
History of	CAD	27% (3)	20% (6)	NS
	AMI	27% (3)	13% (4)	NS
	PCI	27% (3)	20% (6)	NS
	CABG	0% (0)	0% (0)	NS
	Heart failure	9% (1)	0% (0)	NS
	AH	54.5% (6)	47% (14)	NS
	Stroke	9% (1)	0% (0)	NS
	Smoking	45.5% (5)	60% (18)	NS
AMI	STEMI	54.5% (6)	60% (18)	NS
	NSTEMI	45.5% (5)	40% (12)	
Number of vessels diseased	1	36.4% (4)	27 % (8)	NS
	2	18.2% (2)	43% (13)	
	3	45.5% (5)	30% (9)	
TIMI before PCI	0	45.5% (5)	40% (12)	NS
	1	27% (3)	6.6% (2)	
	2	9% (1)	6.6% (2)	
	3	18.2% (2)	47% (14)	
TIMI after PCI	0	0% (0)	0% (0)	NS
	1	0% (0)	3.3% (1)	
	2	0% (0)	0% (0)	
	3	100% (11)	96.7% (29)	

AH — arterial hypertension; AMI — acute myocardial infarction; CAD — coronary artery disease; CABG — coronary artery bypass grafting; MI — myocardial infarction; MTH mild therapeutic hypothermia; NS — not significant; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction

Figure 1. Platelet reactivity over time assessed with multiplate in myocardial infarction (MI) patients treated with primary percutaneous coronary intervention with (n = 9) versus without (n = 30) out-of-hospital cardiac arrest and mild therapeutic hypothermia (MTH) after loading dose of ticagrelor.

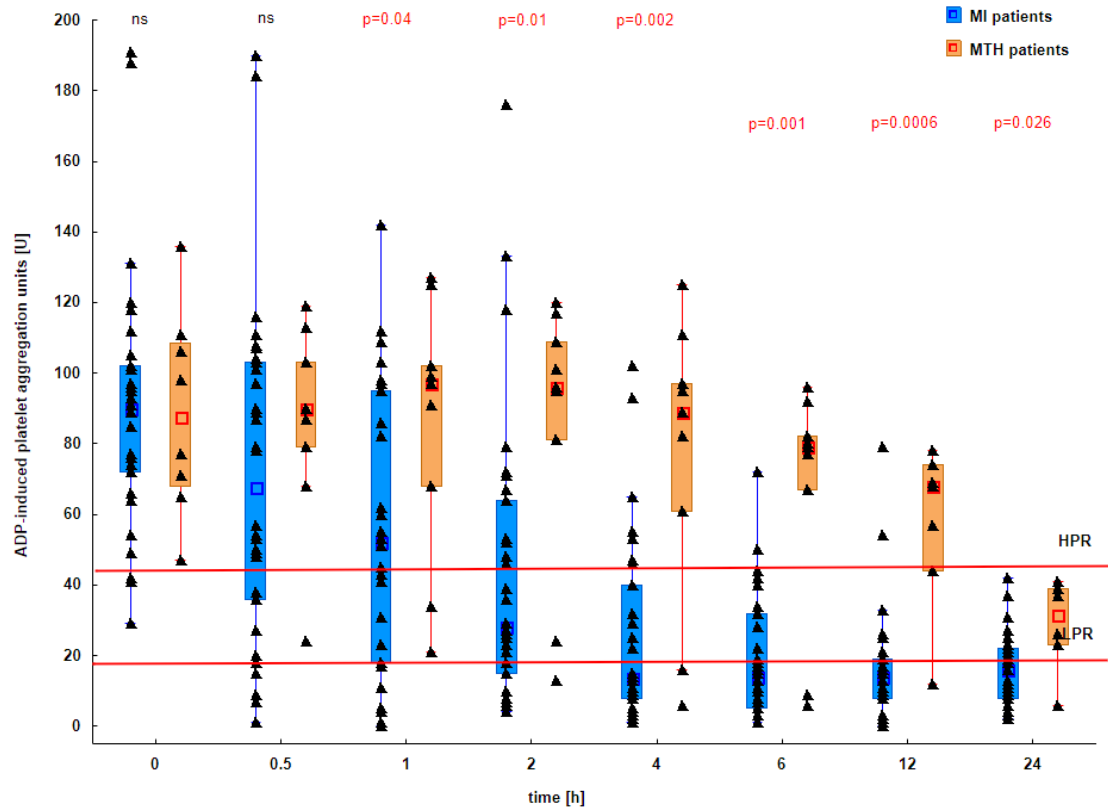


Figure 2.

Proportion of patients with high platelet reactivity (HPR) over time assessed with multiplate in myocardial infarction (MI) patients (blue bars) versus mild therapeutic hypothermia (MTH) patients (red bars) after loading dose of ticagrelor.

