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Effects of intravenous lysine acetylsalicylate versus oral aspirin on platelet responsiveness in patients with ST-segment elevation myocardial infarction: the ECCLIPSE-STEMI trial

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Abstract

Prasugrel and ticagrelor, new P2Y12-ADP receptor antagonists, are associated with greater pharmacodynamic inhibition and reduction of cardiovascular events in patients with an acute coronary syndrome. However, evidence is lacked about the effects of achieving faster and stronger cyclooxygenase inhibition with intravenous lysine acetylsalicylate (LA) compared to oral aspirin. Recently, we demonstrated in healthy volunteers that the administration of intravenous LA resulted in a significantly reduction of platelet reactivity compared to oral aspirin. Loading dose of LA achieves platelet inhibition faster, and with less variability than aspirin. However, there are no data of this issue in patients with an ST-segment elevation myocardial infarction (STEMI). This is a prospective, randomized, multicenter, open platelet function study conducted in STEMI patients. Subjects were randomly assigned to receive a loading dose (LD) of intravenous LA 450 mg plus oral ticagrelor 180 mg, or LD of aspirin 300 mg plus ticagrelor 180 mg orally. Platelet function was evaluated at baseline, 30 min, 1 h, 4 h and 24 h using multiple electrode aggregometry and vasodilator-stimulated phosphoprotein phosphorylation (VASP). The primary endpoint of the study is the inhibition of platelet aggregation (IPA) after arachidonic acid (AA) 0.5 mM at 30 min. Secondary endpoints were the IPA at 1, 4, and 24 h after AA, and non-AA pathways through the sequence (ADP and TRAP). A total of 32 STEMI patients were randomized (16 LA, 16 aspirin). The inhibition of platelet aggregation after AA 0.5 mM at 30 min was greater in subjects treated with LA compared with aspirin: 166 vs. 412 respectively (p = 0.001). This differential effect was observed at 1 h (p = 0.01), but not at 4 and 24 h. Subjects treated with LA presented less variability and faster inhibition of platelet aggregation wit AA compared with aspirin. The administration of intravenous LA resulted in a significantly reduction of platelet reactivity compared to oral aspirin on ticagrelor inhibited platelets in patients with STEMI. Loading dose of LA achieves an earlier platelet inhibition, and with less variability than aspirin.
Trial Registration: Unique identifier: NCT02929888; URL: http://www.clinicaltrials.gov

Keywords Platelets · Lysine acetylsalicylate · Aspirin · Acute coronary syndrome

Highlights

- Antiplatelet therapy plays a key role in patients with ST-segment elevation myocardial infarction (STEMI)
- Although potent P2Y12-ADP receptor inhibitor-drugs have shown a reduction in cardiovascular outcomes in this scenario, evidence is lacked about achieving faster cyclooxygenase inhibition
- The results of our study suggest that, compared with oral aspirin, intravenous lysine acetylsalycilate significantly

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achieved an earlier platelet inhibition in STEMI patients, with less variability
- Larger studies are warranted to assess whether this strategy could decrease cardiovascular ischemic events in this scenario

Introduction

In patients with an acute coronary syndrome (ACS), platelets play a key role, particularly in the early phases of the disease [1, 2]. Activated platelets release thromboxane A_2 (TXA_2), adenosine diphosphate (ADP) and adenosine triphosphate (ATP), stimulating platelet activation and aggregation processes [3]. Thus, antiplatelet therapy is the cornerstone of treatment for patients with coronary artery disease [4]. Currently, the combination of aspirin, an irreversible inhibitor of cyclooxygenase (COX) and a P2Y12-ADP receptor inhibitor, is the antiplatelet treatment of choice in patients with ACS, where a fast and strong platelet inhibition is needed [5, 6]. Although prasugrel and ticagrelor have shown a better profile than clopidogrel by reducing cardiovascular outcomes in patients with ACS [7–11], evidence is lacked about achieving faster and stronger COX inhibition. In fact, current guidelines of management of ACS only recommend loading dose of oral non-enteric-coated aspirin (162–325 mg), and intravenous use only when oral ingestion is not possible [5, 6].

Lysine acetylsalicylate (LA) is a soluble salt that, shortly after being administered, is converted into acetylsalicylic acid, which is metabolized in the liver to salicylic acid (active form) [12, 13]. LA presents potent antiplatelet compound with fewer gastrointestinal adverse effects than aspirin and has the unique property of being able to be administered both orally and intravenous [14]. Some studies have compared aspirin with LA in both, healthy volunteers and patients with stable coronary artery disease, and showed similar or higher effectiveness on platelet inhibition with LA [15, 16]. Recently, it has demonstrated that the administration of intravenous LA resulted in a significantly reduction of platelet reactivity compared with aspirin orally in healthy volunteers; moreover, LA achieves faster platelet inhibition, and with less intra- and interindividual variability than aspirin [17]. However, there is no data about this finding in the setting of ST-segment elevation acute myocardial infarction (STEMI) patients, where early platelet inhibition could be associated with a reduction in cardiovascular events [18–20].

Therefore, the present study aims to analyze the effects of combined administration of intravenous LA versus aspirin orally on platelet aggregation, and to assess whether the administration of these different drug regimens affect the time to onset of platelet inhibition.

Methods

Patient population

The ECCLIPSE-STEMI ("*Impact of intravenous Lysine Acetylsalicylate versus oral Aspirin on in Patients with ST-segment Elevation Myocardial Infarction*", www.controlled-trials.com number NCT02929888) trial was a prospective, randomized, multicenter, open, pharmacodynamic platelet function study in patients with an acute myocardial infarction. Patients were enrolled if they were ≥ 18 years-old and were admitted with a diagnosis of STEMI by the emergency units, defined by an episode of chest pain or equivalent symptoms, associated to ECG typical disorder (persistent elevation of ST-segment ≥ 1 mm in frontal leads, or ≥ 2 mm in precordial leads in at least 2 adjoining leads; or new onset left bundle branch block). Exclusion criteria included: known allergies to aspirin, clopidogrel, prasugrel or ticagrelor, cardiogenic shock or hemodynamic instability, recent antiplatelet therapy (< 14 days), including nonsteroidal anti-inflammatory drugs (NSAIDs.), oral anticoagulation, any active bleeding or blood dyscrasia, recent gastrointestinal bleeding (< 6 months prior to inclusion), recent history of stroke or intracranial bleeding (< 6 months prior to inclusion), known anemia, thrombopenia or severe chronic kidney/liver disease, any known active neoplasm, or pregnant females. The study complied with the Declaration of Helsinki and it was approved by the Ethical Committee of the San Carlos University Hospital [21]. All patients gave their written informed consent to participate in the study. A clinical research organization (CRO) was contracted to hold the data and perform the data analysis after data lock. An independent data safety monitoring committee was instituted for adjudication of adverse clinical events.

Study design and randomization

Patients were randomly allocated in a 1:1 fashion to receive 450 mg intravenous LA or 300 mg of oral aspirin (non-enteric coated formulation). Both groups will receive routine care in the setting of the STEMI clinical practice guidelines, including concomitant administration of a potent P2Y12 ADP-receptor inhibitor: ticagrelor (this drug was selected because it is the P2Y12 ADP-receptor inhibitor available in our emergency care setting). Blood samples will be extracted at baseline (before the administration of antithrombotic drugs), at 30 min, 1, 4, and at 24 h so as to measure platelet function. All subjects underwent standard cardiology care including, unless contraindicated, primary percutaneous coronary intervention (PCI). Use of glycoprotein (GP) IIb/IIIa inhibitors and choice of anticoagulant were left to the criteria of the treating physician.

Concomitant treatments, such as beta-blockers, angiotensin-converting enzyme -inhibitors and statins were used according to current clinical guidelines [5, 6]. The ECCLIPSE-STEMI trial started including patients in June 2017, and recruitment were extended until December 2020 due to COVID-19 pandemic situation.

Platelet function testing

Blood samples were collected from an antecubital vein using a 21-gauge needle into 5 ml plastic tubes containing hirudin (25µg/mL) after randomization and each of the previously specified set time points. First 3 ml of blood were discharged to avoid spontaneous platelet activation. All samples were processed within 1 h by researchers that were blinded to the treatment assigned.

Platelet aggregation

Platelet aggregation were assessed using multiple electrode aggregometry (MEA), in whole blood with the Multiplate™ analyzer (Roche Diagnostics, Basel, Switzerland) as previously described [22]. This instrument assesses the change in impedance caused by the adhesion of platelets onto sensor units formed by silver-covered electrodes. Curves were recorded for 6 min, and platelet aggregation was determined as area under the curve of arbitrary aggregation units (AU*min). In the present investigation, 0.5 mM arachidonic acid (AA) were used to evaluate COX inhibition, 6.4 µM ADP was used as agonist to evaluate P2Y12 inhibitors responsiveness, and thrombin receptor-activated peptide (TRAP) 32 µM were used to stimulate thrombin-dependent platelet aggregation. Inhibition of platelet aggregation (IPA) was defined as the relative percent decrease in maximal aggregation and was calculated as [(baseline aggregation response—aggregation at the different timepoints of the study)/baseline aggregation response] × 100.

Platelet P2Y12 reactivity index (PRI)

The PRI was determined through assessment of vasodilator stimulated phosphoprotein (VASP) phosphorylation according to standard protocols [23]. In brief, VASP phosphorylation was measured by quantitative flow cytometry (Gallios cytometer Beckman Coulter, Miami, Florida) using commercially available labeled monoclonal antibodies (Biocytex Inc., Marseille, France). The PRI was calculated after measuring the mean fluorescence intensity (MFI) of VASP phosphorylation levels following challenge with prostaglandin E_1 (PGE_1) and prostaglandin E1 plus ADP. PGE_1 increases VASP phosphorylation levels through stimulation of adenylate cyclase, while ADP binding to purinergic receptors leads to the inhibition of adenylate cyclase. Therefore, the addition of ADP to prostaglandin E_1-stimulated platelets reduces levels of prostaglandin E_1-induced VASP phosphorylation. PRI = [(MFI PGE1) − (MFI PGE1 + ADP)/(MFI PGE1)] × 100. Elevated PRI values are indicative of upregulation of the $P2Y_{12}$ signaling pathway.

Endpoints and sample size

The primary endpoint of the study was the inhibition platelet aggregation (IPA) responses to AA stimuli 30 min after administration of study drugs. Secondary endpoints were the IPA at 1, 4 and 24 h after AA, and non-AA pathways through the sequence. Another secondary endpoints were the cardiovascular outcomes (death, reinfarction, stroke) and bleeding events during admission. To estimate the sample size, and according to previous pharmacodynamics studies, we hypothesized a 27% mean reduction in the primary endpoint following treatment with intravenous LA compared with oral aspirin [15–17]. Therefore, at least 60 subjects would be required to provide a 80% power to detect statistical differences between groups with a two-sided ∝ level of 0.05. Given that the effect size found was larger than initially considered for the primary objective, the contrast finally had sufficient power (more than 85%) to detect differences with an n = 16 size in each group.

Statistical analysis

Endpoints were analyzed for all recruited patients in an intention to treat analysis. Statistical analysis will be performed by an independent investigator, blinded to the study group assignment. Variables were analyzed for a normal distribution with the Kolmogorov–Smirnov test. Normally distributed variables are presented as mean ± standard deviation and were compared using the Student t test. Variables that did not follow a normal distribution are presented as median and interquartile range and were compared with the Mann–Whitney U test. Categorical variables are expressed as frequencies and percentages and were compared with the $\chi 2$ test or the Fisher exact test when at least 25% of values showed an expected cell frequency below 5. Confidence intervals (CI) and all test of statistical significance for treatment comparisons were evaluated at a two-tailed significance level of 0.05. All analyses of platelet function were conducted in all randomized subjects who received at least one dose of study drug. Statistical analysis was performed using SPSS/PC 17 (SPSS Inc. Chicago, Illinois).

Table 1 Baseline characteristics according to treatment group

	Lysine acetylsalicylate (n = 16)	Aspirin (n = 16)	p-value
Age (yrs), mean ± SD	64.2 ± 9.8	64.3 ± 8.9	NS
Male, n (%)	9 (56.3)	8 (50.0)	NS
Risk factors, n (%)			
Current smoking	7 (43.8)	6 (37.5)	NS
Hypertension	6 (37.5)	6 (37.5)	NS
Dyslipidemia	7 (43.8)	8 (50.0)	NS
Known DM	2 (12.5)	3 (18.8)	NS
Obesity (BMI > 30 kg/m^2)	2 (12.5)	4 (25.0)	NS
Medical history, n (%)			
Previous stroke	1 (6.3)	0 (0.0)	NS
Previous COPD	2 (12.5)	1 (6.3)	NS
Chronic kidney disease	1 (6.3)	1 (6.3)	NS
Clinical and angiographic characteristics, n (%)			
Anterior STEMI	9 (56.3)	8 (50.0)	NS
Killip class ≥ 2	2 (12.5)	1 (6.3)	NS
Left ventricular ejection fraction (%), mean ± SD	53.7 ± 12.4	54.7 ± 12.9	NS
FMC to balloon (min), median (IQR)	91.5 (69.8–106.0)	86.0 (70.3–111.0)	NS
Multivessel disease	6 (37.5)	7 (43.8)	NS
Laboratory data			
Hematocrit (%)	42.9 ± 3.1	42.5 ± 5.3	NS
Platelet count (1000/mm^3)	257.4 ± 82.4	256.6 ± 63.78	NS
Creatinine clearance (mL/min)*	85.4 ± 14.2	84.5 ± 16.8	NS
HbA1c (%), median (SD)	5.5 (0.8)	5.6 (0.6)	NS
LDL-c (mg/dL), median (SD)	118.0 ± 33.1	123.9 ± 25.5	NS
Peak troponin I (ng/mL), median(IQR)	74.9 (22.9–126.5)	77.9 (33.2–163.8)	NS

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *FMC* first medical contact. *HbA1c* glycated haemoglobin. *IQR* interquartile range, *LDL-c* low density lipoprotein-cholesterol. *SD* standard deviation. *STEMI* ST elevation myocardial infarction. * assessed by de Crockcroft & Gault formula

Results

Patient population

A total of 32 patients with STEMI were randomized (16 in intravenous LA group and 16 in oral aspirin group). Baseline demographics, clinical characteristics, laboratory data and angiographic findings of both groups are shown in Table 1. There were no significant differences between groups. Table 2 shows in-hospital management and cardiovascular outcomes, and no differences were found between LA and aspirin group.

Platelet function profiles

There were no differences in platelet function at baseline between intravenous LA plus ticagrelor and oral aspirin plus ticagrelor groups with all platelet function test assessed (Table 3). Platelet reactivity at 30 min after AA 0.5 mM was significantly lower in patients treated with intravenous LA compared with oral aspirin: 166.0 (64.5–247.0) vs. 412.0 (241.0–589.0), p = 0.001. These results were observed at 1 h [148.0 (86.0–188.5) vs. 221.0 (170.0–311.0), p = 0.013], but not at 4 h and 24 h. Figure 1 shows IPA with AA 0.5 mM at any time points.

Table 2 In-hospital management and adverse outcomes according to treatment group

	Lysine acetylsalicylate (n = 16)	Aspirin (n = 16)	p-value
Coronary revascularization procedures, n (%)			
Primary PCI	15 (93.8)	14 (87.5)	NS
CABG	0 (0.0)	1 (6.3)	NS
No revascularization	1 (6.3)	1 (6.3)	NS
Drug therapy during hospitalization, n (%)			
GP IIb/IIIa inhibitors	2 (12.5)	3 (18.8)	NS
Unfractioned heparin	14 (87.5)	13 (81.3)	NS
Enoxaparin	2 (12.5)	3 (18.8)	NS
Beta-blockers	16 (100.0)	15 (93.8)	NS
ACE inhibitors/ARB	12 (75.0)	11 (68.8)	NS
Statins	16 (100.0)	16 (100.0)	NS
Adverse in-hospital outcomes, n (%)			
Death	0 (0.0)	0 (0.0)	N/A
Stent thrombosis	0 (0.0)	1 (6.3)	NS
Ventricular arrhythmias	1 (6.3)	0 (0.0)	NS
Cardiogenic shock	1 (6.3)	2 (12.5)	NS
Complete AV block	1 (6.3)	1 (6.3)	NS
Major bleeding	1 (6.3)	1 (6.3)	NS

ACE angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *AV* auriculo-ventricular; *CABG* coronary artery bypass graft, *GP* glycoprotein, *IQR* interquartile range, *NS* non-significant, *PCI* percutaneous coronary intervention

Platelet function profiles according to P2Y12-dependent pathway and thrombin-dependent platelet aggregation were tested with ADP 6.4 µM and TRAP 32 µM respectively. There were no differences between intravenous LA and oral aspirin groups at any time points (p = NS). These results were similar when exploring platelet activation with PRI.

Figure 2 shows individual subject antiplatelet response after AA 0.5 mM at baseline, 30 min, 1, 4 and 24 h. Subjects treated with LA presented less variability and faster decrease in platelet inhibition compared with aspirin group.

Discussion

Antiplatelet therapy plays a pivotal role in the management of STEMI patients. Current practical guidelines recommend in these patients the combination of aspirin and a P2Y12 inhibitor (preferably prasugrel/ticagrelor than clopidogrel, if no contraindicated) [6]. Specifically, and according to these recommendations, aspirin should be given orally including chewing, or intravenous (if oral ingestion is not possible) to ensure complete inhibition of thromboxane A2-dependent platelet aggregation. However, it is unclear whether the administration of intravenous antiplatelet in this scenario leads to a better prognosis [24]. This is the first randomized trial to analyze the pharmacodynamic effects of intravenous LA compared to aspirin orally in patients with STEMI. In particular, the results of the study show that intravenous LA was associated with higher platelet inhibition than oral aspirin group. Further, the administration of intravenous LA resulted in a rapid and marked reduction on platelet reactivity by 30 min compared to oral aspirin. Finally, LA achieved a more consistent platelet inhibition and less inter- and intraindividual variability.

Interestingly, the results of our study were consistent with previous report in healthy volunteers [17]. Thus, the STEMI scenario is associated with a prothrombotic and inflammation state, and an early platelet inhibition reveals as a key role in the treatment of acute coronary disease. Despite of this unfavorable situation, patients treated with intravenous LA showed faster platelet inhibition. Due to a lower sample size, the study was not designed to detect differences in cardiovascular outcomes, and more studies are needed to know whether a faster platelet inhibition in STEMI patients could be associated with a reduction in cardiovascular events [18–20].

It has been hypothesized that LA not only reduces platelet reactivity when COX pathway was assessed, but also showed and early and faster reduction with other platelet inhibition receptors [17]. Although in healthy volunteers intravenous LA compared with oral aspirin showed a significant reduction in thrombin-dependent platelet pathway aggregation, the ECCLIPSE-STEMI trial did not find significant differences in any stage of the analysis.

Current investigation concentrates on the field of $P2Y_{12}$-ADP platelet receptor inhibition. Prasugrel and ticagrelor are characterized by more prompt, potent and predictable antiplatelet effects and greater clinical efficacy than clopidogrel [10, 11]. However, these drugs also present limitations, including a delayed antiplatelet effect, particularly in the setting of STEMI. In the ECCLIPSE-STEMI trial, all patients were treated with loading dose of ticagrelor 180 mg, and differences in platelet reactivity were shown despite a faster ADP-P2Y12 inhibition. Therefore, these findings show that, despite of a high ticagrelor platelet inhibition, intravenous LA could reduce platelet reactivity faster than aspirin, which could have clinical implications.

Other intravenous antiplatelet agents have been assessed in the setting of the ACS, such as Glycoprotein IIb/IIIa inhibitors or cangrelor [25–27]. However, current STEMI clinical guidelines did not recommend the routine use of these drugs, and only cangrelor could be considered in patients not pre-treated with oral P2Y12 inhibitors at the time of primary percutaneous coronary intervention [6]. In the ECCLIPSE-STEMI trial, only 5 patients (2 in LA and 3 in aspirin group) received downstream intravenous abciximab, none of them in the first 60 min after study drug

Table 3 Platelet function profiles according to treatment assigned

	Lysine acetylsalicylate (n = 16)	Aspirin (n = 16)	p-value
AA 0.5 mM (%)			
Baseline PR	635.0 (334.0–10.009.0)	574.0 (390.0–805.0)	0.802
30 min PR	166.0 (64.5–247.0)	412.0 (241.0–589.0)	0.001
1 h PR	148.0 (86.0–188.5)	221.0 (170.0–311.0)	0.013
4 h PR	124.0 (23.0–129.0)	81.5 (60.0–93.0)	0.774
24 h PR	107.0 (46.0–180.0)	147.5 (92.0–211.0)	0.228
ADP 6.4 µM (%)			
Baseline PR	351.5 (221.5–683.0)	507.0 (313.0–700.0)	0.464
30 min PR	313.0 (214.0–499.0)	419.0 (290.5–598.0)	0.609
1 h PR	232.5 (166.5–452.5)	351 (188.0–478.0)	0.407
4 h PR	154.0 (122.3–255.0)	127.5 (114.0–204.0)	0.391
24 h PR	152.0 (93.0–213.0)	137.5 (89.0–191.0)	0.827
TRAP 32 µM (%)			
Baseline PR	678.0 (387.5–904.0)	805.0 (651.0–947.0)	0.272
30 min PR	617.0 (481.0–758.0)	874 (819.0–1023.0)	0.057
1 h PR	826.0 (598.0–964.5)	729.0 (568.0–961.0)	0.733
4 h PR	462.0 (266.0–731.0)	630.5 (435.0–727.0)	0.568
24 h PR	520.0 (320.5–797.0)	561.5 (303.0–710.0)	0.820
PRI (%)			
Baseline	71.8 (48.8–76.8)	71.9 (56.1–80.7)	0.864
30 min	55.8 (46.8–80.9)	67.8 (55.1–82.4)	0.492
1 h	23.0 (14.6–82.1)	39.4 (6.4–88.2)	0.868
4 h	22.4 (10.6–29.8)	17.3 (6.5–30.5)	0.423
24 h	14.4 (1.36–34.8)	13.8 (4.1–25.4)	0.843

Values are median (interquartile range). *AA* arachidonic acid. *ADP* adenosin diphosphate. *IPA* inhibition of platelet aggregation. *TRAP* thrombin receptor-activated peptide. *PR* platelet reactivity. *PRI* platelet P2Y12 reactivity index

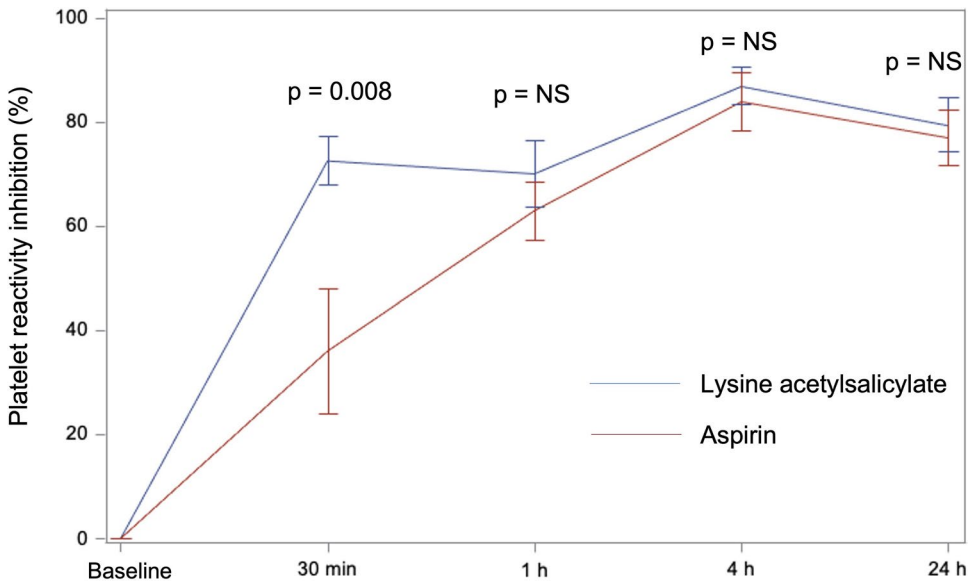

Fig. 1 Mean inhibition of platelet aggregation (IPA) responses to Arachidonic Acid (AA) 0.5 mM at timeline 0 (baseline), 30 min, 1 h, 4 h, and 24 h after Lysine Acetylsalicylate 450 mg iv (n = 16), or Aspirin 300 mg orally (n = 16)

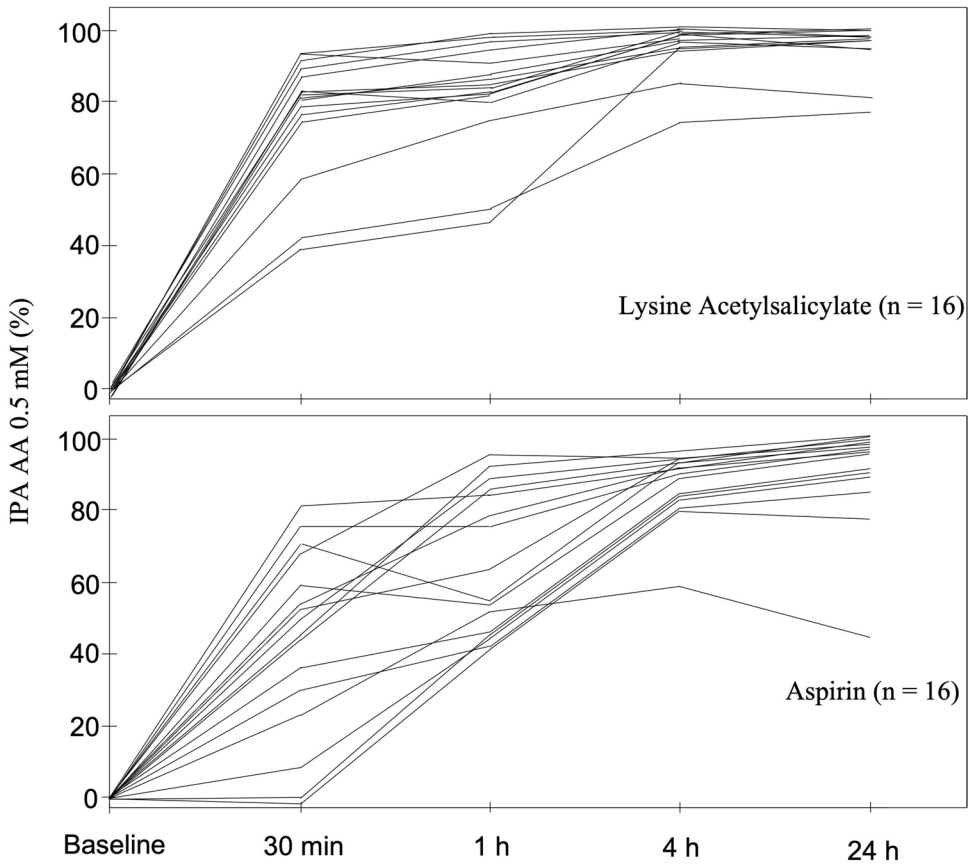

Fig. 2 Individual subject inhibition of platelet aggregation (IPA) responses to Arachidonic Acid (AA) 0.5 mM stimuli at baseline, 30 min, 1 h, 4 h and 24 h after Lysine Acetylsalicylate 450 mg iv (upper panel), or Aspirin 300 mg orally (lower panel)

administration. The effect of Glycoprotein IIb/IIIa inhibitor in these patients did not affect platelet function test at 30 and 60 min, although we could not dismiss some biases in the rest of study timepoints.

This study has some limitations. First, the trial enrolled patients with STEMI, and this fact may limit the generalization to clinical patient population with another cardiovascular disease. Second, the relation between clinical outcomes and the speed of onset and magnitude of platelet inhibition with LA is unknown. Moreover, this study has a small sample size (eventually less patients than those initially planned) and the final results should be considered carefully. Finally, the present study was not designed to evaluate maintenance doses. However, protocol design and statistical analyses reinforced the value of the results obtained, which suggested a pharmacodynamic benefit of intravenous LA compared with oral aspirin.

Conclusions

The administration of intravenous LA resulted in a significantly reduction of platelet reactivity compared to oral aspirin on ticagrelor inhibited platelets in patients with STEMI. Loading dose of LA achieves an earlier platelet inhibition, and with less variability than aspirin.

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Data Availability The data that support the findings of this study are available on request from thecorresponding author, on reasonable request.

Declarations

Conflict of interest The authors declare that there is no conflict of interest in this manuscript.

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