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Letters

Ticagrelor Crushed Tablets Administration in STEMI Patients

The MOJITO Study

In healthy volunteers, 300 mg clopidogrel administered crushed via a nasogastric tube results in faster and greater bioavailability of the drug compared with whole tablets administered orally (1). Recently, Crean et al. (2) reported that ticagrelor tablets could be easily crushed and prepared for oral and nasogastric tube administration, delivering the full dose of the original tablet.

The MOJITO (Mashed Or Just Integral pill of TicagrelOr) study was a prospective, 4-center, international, randomized, active-controlled study with the aim to evaluate the superiority of ticagrelor crushed pills versus integral tablets of equal dose in decreasing platelet reactivity in $P2Y_{12}$-naive, ST-segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention. The local ethics committee approved the study, which was registered on ClinicalTrials.gov (NCT01992523). All patients gave informed consent. Following exclusions, 82 patients were randomized to either a crushed ticagrelor 180-mg loading dose (LD) or oral integral tables of equal dose before primary percutaneous coronary intervention. Crushed tablets were prepared placing 2 ticagrelor pills in a mortar and mashing for 60 s using a pestle (2). The total contents of the mortar was transferred to the dosing cup, 50 ml of purified water was added, and the suspension was mixed up before drinking. Platelet function testing was performed with VerifyNow (Accumetrics, San Diego, California) at baseline and at 1, 2, 4, and 8 h, and the results are reported in $P2Y_{12}$ reaction units (PRU) (3). High-platelet reactivity (HPR) was defined as a PRU >208. The primary endpoint was PRU 1 h after LD.

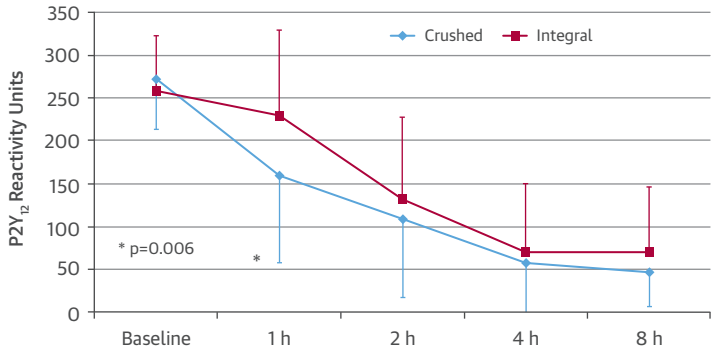
A forward stepwise binary logistic regression analysis was used to evaluate the independent contribution of clinical characteristics to HPR at 1 h with certain variables entered into the model, including age (years), body mass index, diabetes mellitus, morphine use, baseline PRU value, and ticagrelor crushed pills. A significance of 0.05 was required for a variable to be included in the multivariate model, whereas 0.10 was the cutoff value for exclusion. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A p value <0.05 was considered to be statistically significant.

Baseline characteristics did not significantly differ between groups. PRU 1 h after the LD was 168 (interquartile range [IQR]: 61 to 251) and 252 (IQR: 167 to 301) in the crushed and integral groups, respectively ($p = 0.006$), with no differences observed at 2, 4, and 8 h (**Figure 1**). HPR was found in 14 (35%) and 26 (63%) patients at 1 h ($p = 0.011$) and in 8 (20%) and 11 (28%) patients at 2 h ($p = 0.431$) in the crushed and integral groups, respectively. Independent predictors of HPR 1 h after LD were morphine use (increased HPR) and crushed ticagrelor tablet administration (decreased HPR). Morphine-treated patients also showed higher 1-h PRU values in the crushed ticagrelor group ($p = 0.001$). Adverse events were not increased by the administration of crushed ticagrelor.

Our study shows, for the first time to our knowledge, that crushed ticagrelor tablet administration in STEMI patients is feasible and provides earlier platelet inhibition compared with standard integral tablets. If this effect translates into fewer acute stent thromboses and into better myocardial reperfusion, it should be assessed in larger studies. All $P2Y_{12}$ receptor antagonists used at the present time in STEMI treatment are only available orally. This is an important limitation in patients with difficulties with swallowing such as the elderly, those patients with prior stroke or dysphagia, or those who have been sedated or intubated. Our study might support the use of crushed ticagrelor in patients unable to swallow.

Our results must be evaluated in light of some limitations. First, the small sample size is certainly the most important limitation. However, we were able to enroll a prospective homogenous population of STEMI patients that mirrors other similar studies, and clinical outcome data were reported only as indicative. The safety profile and patient tolerance of crushed ticagrelor tablets should be definitively tested in broader studies. Second, to confirm

FIGURE 1 Platelet Inhibition Over Time



Platelet reactivity was assessed at baseline, 1, 2, 4, and 8 h after a 180-mg ticagrelor loading dose in patients treated by crushed tablets **(diamonds)** or integral tablets **(squares)**. Data are expressed as mean ± SD.

enhanced drug absorption, a pharmacokinetic analysis could also have been performed. Higher plasma levels of ticagrelor and its active metabolite with crushed tablets as compared with integral tablets have been recently reported in healthy subjects (4). Finally, unmeasured confounder and overfitting risks cannot be excluded in our multivariable model.

These limitations notwithstanding, the present study provides unique and potentially important insights in the treatment of STEMI patients.

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TGFβR1 Inhibition Blocks the Formation of Stenosis in Tissue-Engineered Vascular Grafts

We previously developed a tissue-engineered vascular graft (TEVG), created by seeding a biodegradable scaffold with autologous bone marrow-derived