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Higher mean platelet volume determined shortly after the symptom onset in acute ischemic stroke patients is associated with a larger infarct volume on CT brain scans and with worse clinical outcome

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ABSTRACT

Objective: Mean platelet volume (MPV) determined shortly after the onset of acute ischemic stroke represents the pre-stroke values. Data on its relationship to stroke severity/outcome have been conflicting. We related MPV to infarct volume on CT brain scans and risk of death/dependence 7 days and 3 months post-stroke.
Methods: MPV (within 30 h since stroke onset), infarct volume (13–83 h since stroke onset) and clinical outcomes were evaluated in 81 consecutive patients (32 men, age 52–91 years, 10 small artery occlusion, 10 large artery atherosclerosis, 29 cardioembolic, 32 multiple probable/possible etiology).
Results: Higher MPV was independently associated with larger ln-infarct volume [estimate 0.259, 95% confidence interval (CI) 0.004–0.513, $P = 0.046$], greater risk of death/dependence 7 days post-stroke [relative risk (RR) = 1.077, 95% CI 1.005–1.115, $P = 0.036$], and greater risk of death/dependence 3 months post-stroke (RR = 1.077, 95% CI 1.001–1.158, $P = 0.048$). Considered covariates: stroke etiology, CT scan timing, platelet count and other hematological parameters, demographic variables, history of cerebrovascular, cardiac or cardiovascular diseases, diabetes, serum chemistry, previous antiplatelet and statin use and treatments delivered after the index event.
Conclusions: Data support the view about MPV as a determinant of severity/outcome of the acute ischemic stroke.

1. Introduction

Larger platelets undergo greater *in vitro* aggregation in response to specific stimuli, release more prothrombotic mediators and are associated with a decreased bleeding time. Hence, greater platelet size, expressed as mean platelet volume (MPV), is considered a marker of increased platelet reactivity [1–3]. A considerable body of experimental evidence documents a role of increased platelet reactivity in the development of various ischemic stroke types [1–4] and it is considered to be a relevant pathophysiological factor in approximately 50% of all strokes [3]. In cross sectional studies, MPV determined shortly after the stroke onset has been more or less consistently higher in acute ischemic stroke patients than in corresponding control subjects [2,3,5–7]. Earlier studies indicated that MPV, defined during thrombopoiesis [2,3], remained stable throughout the platelet life span of around 10 days and was not affected by the stroke [2,3,7]. In a recent study [8], however, MPV determined 12–48 h post-stroke was found mildly (by 2–4%) but significantly lower than MPV determined 2–6 days later, suggesting that stroke might have contributed to increased MPV likely due to an accelerated thrombopoiesis resulting in release of immature and larger platelets. Still, considering that even when accelerated thrombopoiesis takes a few days [2], MPV determined early post-stroke (e.g., within the first 48 h) primarily represents the pre-stroke status [2,3]. Taken together with the fact that larger MPV was an independent risk factor for ischemic stroke in a prospective cohort study (sub-study of the PROGRESS trial) in patients with a history of stroke or transitory ischemic attack [9], the above observations support a view about causal relationship between MPV and stroke. The relationship between MPV and stroke severity, on the other hand, is less clear. Two out of four studies relating MPV determined within 2–3 days after acute ischemic stroke onset and severity of clinical symptoms/outcomes have indicated their association [6,10], whereas the remaining two have not [5,7]. Although in some acute ischemic stroke patients CT brain scans may fail to

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show visible lesions, infarct volume determined from CT scans is a biomarker that correlates rather well with the symptom severity/stroke outcome [11–13]. In the present study, we related MPV determined shortly after the stroke onset to infarct volume determined on CT brain scans, as well as to clinical outcome assessed by the means of the modified Rankin scale (mRS) 7 days after the stroke. Clinical outcome (mRS) was also assessed 3 months after the stroke and its relationship to MPV was considered as a secondary objective.

2. Patients and methods

Candidates for inclusion in this observational study were consecutive acute ischemic stroke patients referring to our institution over a predefined 5-month period. They all underwent the same standard in-house procedure for patients with suspected cerebrovascular incidents that included routine laboratory tests on admission (blood/urine chemistry and hematology) and a CT brain scan. Other diagnostic procedures were undertaken when indicated. Patients were included in the present analysis when the following criteria were met: (1) Admission/MPV determination within 36 h since the stroke onset. We assumed that MPV determined within this period would not be affected by the vascular event and would represent the pre-stroke situation [2,3,10]. (2) CT scan performed no later than 84 h since the symptom onset with visible fresh ischemic lesions. In some acute ischemic stroke, patients CT fails to identify fresh ischemic lesions regardless of the scan timing, but the probability of that appears the greatest when scanning is done very early after the symptom onset [11,12]. However, delaying CT scanning on purpose would not be a "good practice" in stroke patients [12]. In our experience and in line with the experience of others [11], most patients are being scanned in the period between 24 and around 90 h after the stroke onset. Therefore, by defining inclusion criteria requiring early admission and CT scanning within 84 h since the symptom onset, we expected: (a) that most patients would be scanned between around 24 and 90 h post-stroke when the probability of not detecting visible lesions is the lowest [11]; (b) that variability of infarct volume due to time-dependent changes observed in some patients as a difference in size between an early (e.g., within the first hours post-stroke) and a later measurement (a week later) [13] would be minimal within this time period. (3) Patients were free of malignancy or sever infectious/inflammatory diseases. (4) Consent was obtained (patients/relatives) for using medical data for research purposes. Local Ethics Committee approved the study.

Overall, 81 out of 147 screened patients were enrolled and were classified by stroke etiology according to the TOAST classification as (at least possible/probable): cardioembolic, small artery occlusion, large artery atherosclerosis, or undetermined–unclassified etiology (multiple probable/possible causes) [14,15]) based on agreement/consensus between two independent investigators. Excluded were: (a) 40 patients (27.2%) due to a lack of fresh visible lesions (mild stroke or/and very early CT scan). This was in line with the reported proportions of patients lacking visible lesions when scanned on the day of stroke onset (39.7%) or between 24 and around 90 h after the symptom onset (between 29.6% and 33%) [11]; (b) 20 patients (13.6%) due to late referrals; (c) three patients due to co-morbidity; (d) for three patients stroke etiology remained unknown, due to "absence of diagnostic tests that would have been essential to uncover the underlying cause" [15].

All CT scans were done using a Siemens Somatom Emotion Duo® apparatus and were evaluated by the same investigator unaware of other patients' particulars. Infarct volumes were calculated as described previously [16] using the manual tracing of the perimeter method [17]. In brief, for a particular patient, all slices were analyzed and two-dimensional lesion surfaces were determined on a workstation with digital tolls providing Hounsfield unit measurements. All infratentorial and supratentorial surfaces were summed up separately and were multiplied by the respective slice thicknesses (3 and 8 mm) to yield respective lesion volumes. The sum of the infratentorial and supratentorial volumes gave the overall approximate infarct volume (in cm^3).

Blood samples (for hematology) were analyzed using Abbott Cell-Dyn® 3700 hematology analyzer (EDTA, <2 h between venipuncture and analysis, stored at room temperature, in order to minimize platelet swelling [10]). Quality control checks during the study period consistently yielded ≤4% intra- and inter-assay variability for platelet parameters.

Modified Rankin scale (mRS, 0 = no symptoms at all, 6 = death) [18] was implemented 7 days and 3 months after the stroke by the same rater.

Infarct volumes were lognormally distributed hence the analysis was performed by fitting linear models (REML estimation) to ln-transformed data. For the analysis of mRS, data were collapsed to two categories: score 0–2 (no to mild symptoms, patient independent) or score 3–6 (patient dependent or dead) [10]. Incidence of dependent/dead patients (score 3–6) was analyzed by modified Poisson regression with robust error variance to yield relative risk (RR). We used SAS for Windows 9.1 (SAS Inc., Cary, NC, USA).

3. Results

All patients included in the present analysis were admitted and all MPV and other laboratory values considered were determined within 30 h since the onset of acute ischemic stroke symptoms. All CT brain scans were performed between 13 and 83 h since the symptom onset. Patients' characteristics are summarized in Table 1.

Only one patient was treated with recombinant tissue plasminogen activator and a total of 56 (69.1%) were started on aspirin after the index event and before clinical evaluation on day 7 post-stroke. Other treatments administered during this period included treatments of co-morbidity (e.g., insulin in 5/15 diabetics, oral antidiabetics for others, antihypertensive/antiarrhythmic drugs, chronic heart failure treatment, only a few treated for post-stroke seizures).

Potential association between MPV and infarct volume (ln-infarct volume) was first tested in a "partially adjusted" model: adjustment for platelet count, as higher MPV was univariately associated with lower platelet counts (Spearman's correlation coefficient −0.385, 95% confidence interval −0.556 to −0.181, $P < 0.001$); stroke etiology, as infarct volume varied considerably by stroke type (Fig. 1A); and CT scan timing, as time has been suggested to influence CT findings, although no major difference in infarct volume was apparent in the three patient subgroups based on the CT scanning window (Fig. 1B). With these "forced independents", higher MPV was associated ($P = 0.039$) with a larger infarct volume (Table 2). Considering the relatively small sample, additional adjustments were selected from variables depicted in Table 1 (except for mRS score) based on "entry" and "stay" cut-off P-values. The final (fully adjusted) model is shown in Table 2. Infarct volume was most prominently determined by stroke etiology, however the association between higher MPV and larger ln-infarct volume remained significant ($P = 0.046$) (Table 2).

Potential association between MPV and the risk of dependence or death (mRS score 3–6) 7 days after the stroke onset was first assessed with adjustment for platelet count and stroke etiology (partial adjustment). Higher MPV was associated with a higher risk of dependence/death ($P = 0.008$) (Table 3). Additional adjustments were selected from variables depicted in Table 1 (except for ln-infarct volume) and use of aspirin after the index event by a similar