



SWEDISH

High Prevalence of Aspirin Resistance in Migraineurs

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Background

Migraineurs have platelet hyperaggregability, which may partially explain their increased risk for stroke and myocardial infarction (MI), particularly in women. Although aspirin is the cornerstone of cost-effective antiplatelet therapy for reducing the risk of stroke in women and MI in men (level of evidence A), the efficacy of aspirin for stroke and MI prevention in migraineurs is unknown. Aspirin resistance refers to an inadequate platelet inhibitory response to aspirin treatment manifested by high post-treatment platelet reactivity (PPR) using ex vivo platelet function tests. It has been attributed to limited and inconsistent therapeutic effects of aspirin in clinical outcomes in populations with cardiovascular disease. To date, there are no published reports of PPR in migraineurs; therefore, the purpose of this study was to estimate the prevalence of PPR in migraineurs who received aspirin 325 mg for 14-21 consecutive days (primary endpoint). The percentage of in vitro platelet inhibition (PPI) achieved at this dosage was assessed as a secondary endpoint.

Methods

Design: Single-group, prospective, intervention study, approved by the Swedish Medical Center (SMC) Institutional Review Board. Non-probability consecutive sampling was used to enroll migraineurs from SMC and the University of Washington Headache Clinic.

Target Population: Subjects aged ≥ 18 years with established diagnosis of active migraine, without aura, confirmed by recent neurological evaluation using International Headache Society (IHS) criteria¹¹⁻¹³ and having ≥ 6 migraine days in the 12 months prior to enrollment.

Methods: Subjects underwent a 14-day washout period of aspirin, NSAIDs, and supplements that affect platelet function (vitamin E ≥ 800 IU per day, omega-3 fatty acids $> 3g$ daily, or willow bark) prior to receiving enteric-coated aspirin 325 mg for 14-21 consecutive days. Subjects were disqualified during washout if they ingested any aspirin or > 1 dose of NSAID within 48 hours of baseline blood collection. Subjects were requalified during intervention if they ingested any non-study aspirin doses or NSAIDs, > 2 doses of ketorolac, or received > 1 dose of post-treatment blood collection. Demographic, migraine frequency, and comorbidity data were obtained from the medical record and/or subject self-report. Migraine burden and disability were assessed by Headache Impact Test (HIT-6) and Migraine Disability Assessment (MIDAS), respectively. Subjects were categorized by aura status and migraine subgroups (episodic vs. chronic vs. medication overuse headache) based on IHS criteria¹¹⁻¹³. Platelet reactivity was measured pre- and post-treatment using the VerifyNow[®] Aspirin Assay (Accumedics, San Diego, CA), which measures platelet aggregation in whole blood following arachidonic acid stimulation. Results are expressed as aspirin reaction units (ARU) in a range from 350-700. Subjects who had baseline ARU ≥ 550 were excluded due to potential underlying platelet dysfunction or non-adherence to washout. For categorical data having PPR (aspirin resistant) PPI ≤ 1 - [(post-treatment ARU - 350)/(baseline ARU - 350)] $\times 100$. Adherence to aspirin regimen was assessed by medication diary, pill count, and serum salicylate measurement.

Statistical Analysis: Data are presented as mean \pm SD or N (%). Chi-square or Fisher's exact test was used to compare categorical data between subjects with and without HPPR. T-test or Mann-Whitney test were used to compare continuous data between groups. Pearson correlation coefficients were calculated to test associations between baseline and post-treatment ARU and subject characteristics. Threshold for statistical significance was set at $\alpha = 0.05$. Bonferroni correction was used for multiple comparisons. A priori sample size calculation was based on secondary clinical relevance in comparison to a test of $\leq 1\%$ in healthy, aspirin-naïve persons. With a sample size of $n = 50$, this study had 88% power to detect a statistically significant result at $\alpha = 0.05$.

Results

Subject Characteristics: Of 312 persons screened over a 24-month period, 66 (21%) subjects were consented. Primary reasons for not enrolling in the study were unwillingness to grant informed consent, did not meet IHS criteria for migraine, unable to tolerate the study protocol, or restricted medication use. Of the 66 subjects, 10 (15%) were disqualified due to baseline ARU > 550 , or ingestion of aspirin or excessive amounts of NSAIDs during washout treatment; thus, 56 subjects began aspirin intervention. Four (7.1%) were lost to follow-up or withdrew consent; two (3.6%) withdrew due to adverse events: melena and severe epigastric pain following NSAID withdrawal. No subjects were withdrawn due to platelet dysfunction. The final sample included 50 subjects (Table 1).

Baseline Characteristic	All Subjects (n=50)	Aspirin Responsive ARU <460 (n=38)	Aspirin Resistant ARU ≥ 460 (n=12)	P Value
Age, years	43 \pm 12	41 \pm 12	47 \pm 12	0.1
Age, years	43 \pm 12	41 \pm 12	47 \pm 12	0.1
Caucasian	45 (90%)	34 (89%)	11 (92%)	0.8
Female	44 (88%)	32 (84%)	12 (100%)	0.3
Body mass index (BMI), kg/m ²	25.9 \pm 5.1	26.6 \pm 5.1	23.6 \pm 4.7	0.08
Hemoglobin, g/dL	13.5 \pm 1.3	13.7 \pm 1.2	12.8 \pm 1.4	0.03
Platelets, 10 ⁹ /L	274 \pm 65	275 \pm 61	270 \pm 78	0.8
Age at migraine onset, yr	20 \pm 13	19 \pm 12	22 \pm 16	0.6
Migraine aura	26 (52%)	21 (55%)	5 (42%)	0.5
Migraine days per month	8 \pm 6	8 \pm 5	8 \pm 7	1.0
Episodic migraine	40 (80%)	31 (82%)	9 (75%)	0.3
Chronic migraine	3 (6%)	3 (8%)	0	
Medication overuse headache	7 (14%)	4 (11%)	3 (25%)	
HIT-6 score	63 \pm 5	63 \pm 5	62 \pm 3	0.5
MIDAS score	35 \pm 29	35 \pm 30	33 \pm 28	0.9

Table 1. Baseline demographic and migraine data. Subjects were grouped according to ARU ≤ 460 and ≥ 460 ; ARU = aspirin reaction units.

Prevalence of High Post-Treatment Platelet Reactivity (Primary Endpoint): Twelve (24%; 95% CI 12-36%) subjects, all female, had HPPR post-treatment and were reclassified as aspirin resistant. Using the more stringent criterion of platelet reactivity ≥ 550 , 4 subjects (8%) had HPPR. Aspirin responsiveness was defined as a post-treatment ARU < 460 and aspirin resistance as a post-treatment ARU ≥ 460 . The prevalence of HPPR was significantly higher in migraineurs with higher baseline hemoglobin levels ($p = 0.03$) and trended toward higher BMI ($p = 0.08$) than aspirin responders (Table 1). Post-treatment ARU was significantly correlated with hemoglobin ($r = -0.39, p = 0.005$) and with BMI ($r = -0.31, p = 0.03$). There were no differences between aspirin responsive and aspirin resistant subjects in age, sex, migraine frequency, or comorbidity status. In comparing migraine subgroups, 22.5% of those with medication overuse headache had aspirin resistance, 22.5% of those with episodic migraine, and 30% of those with chronic migraine (51% vs. 42%, respectively, $p = 0.5$).

Prevalence of Percent Platelet Inhibition $< 60\%$ (Secondary Endpoint): Twelve subjects (24%) had inadequate PPI ($< 60\%$) following aspirin 325 mg for 14-21 consecutive days. Eleven of these subjects (92%) also had HPPR. The association between HPPR and inadequate PPI was highly significant (Figure 1; $p < 0.001$). PPI was significantly correlated with hemoglobin ($r = -0.37, p = 0.008$) and BMI ($r = -0.35, p = 0.01$).

Characteristic	Aspirin Responsive ARU <460 (n=38)	Aspirin Resistant ARU ≥ 460 (n=12)	P Value
Baseline ARU	647 \pm 26	650 \pm 18	0.7
Post-treatment ARU	417 \pm 18	520 \pm 41	<0.001
Percent platelet inhibition	77.1 \pm 7.5%	43.3 \pm 13.4%	<0.001
Serum salicylate, μ g/mL	32.7 \pm 18.6	26.9 \pm 14.9	0.3
Number of days on aspirin	17 \pm 2	16 \pm 3	0.4
Hours between final aspirin dose and post-treatment blood collection	6 \pm 3	8 \pm 11	0.6

Table 2. Study results. Subjects were grouped on the presence or absence of aspirin resistance (ARU ≥ 460); ARU = aspirin reaction units.

Conclusion

Results of this single-center, prospective study suggest that a high proportion of migraineurs (24%; 95% CI 12-36%), particularly women, have diminished in vitro platelet reactivity to aspirin treatment compared to healthy persons (0%)¹⁵ and those with coronary artery disease (3.2%)¹⁶. Further study is needed to confirm the prevalence of aspirin resistance in migraineurs and to identify possible genetic or physiologic mechanisms to explain sex-based differences. The findings may have important clinical implications in managing migraine with antiplatelet therapy to prevent stroke and MI, particularly in women with migraine aura, who have an increased risk of stroke¹⁷ and assess the potential need to explore adjunct, combination or alternative antiplatelet therapy.

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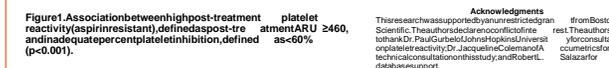


Figure 1. Association between high post-treatment platelet reactivity (aspirin resistant), defined as post-treatment ARU ≥ 460 , and inadequate percent platelet inhibition, defined as $< 60\%$ ($p < 0.001$).