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PLATELET RESISTANCE TO ANTI-AGGREGATING EFFECT OF ACETYLSALICYLIC ACID IN SOLID TUMOR PATIENTS

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Summary

The anti-aggregating effect of acetylsalicylic acid (ASA 100 mg/day and 200 mg/day) was monitored in platelets of 351 solid tumor patients. As ASA increases the aggregation time, its anti-aggregating effect plays an important role in the prevention of thrombosis. Measurements were performed using the Siemens PFA-100 aggregometer with a collagen/EPI test cartridge. The mean age of patients was 64.33 ± 11.67 years. Among them, there were 74 (21.08%) male and 277 (78.91%) female patients suffering from head and neck tumors - 34 pts (9.69%), breast cancer - 222 pts (63.2%), lung cancer - 4 pts (1.14%), abdominal cancer - 54 pts (15.4%), urinary - 4 pts (1.14%), and genital tract cancer - 33 pts (9.4%). Aggregation levels >160 seconds show the ASA effect on circulating platelets. The anti-aggregating effect of ASA 100 mg/day reported in 142 (40%) pts was absent in 209 (60%) pts. The mean anti-aggregating effect of ASA 100 mg/day for male and female patients was 169.29 ± 79.54 and 168.51 ± 69.71 seconds, respectively. No statistically significant difference was found between the male and female platelet aggregation results (p = 0.759). Interindividual variability in aggregation profiles was observed with the coefficient of variation CV = 41-47%. From the group not responding to ASA 100 mg/day, 40 patients were singled out to receive ASA 200 mg/day; of them 17 (42%) were responsive, and 23 (58%) patients were not responsive. No statistically significant difference was found between the two measurements carried out on samples from the same 38 patients with a 1-month interval (p = 0.063) to show the intraindividual stability of platelet aggregation. Whereas the anti-aggregating effect of both ASA 100 mg/day and 200 mg/day has been shown in only 40% patients, dose tailoring based on the individual aggregation result is recommended.

KEYWORDS: *tumors, aggregation resistance, acetylsalicylic acid, PFA-100 aggregometer*

REZISTENTNOST TROMBOCITA BLESNIKA SA SOLIDNIM TUMORIMA NA ANATIAGREGACIJSKI UČINAK ACETILSALICILNE KISELINE

Sažetak

Praćen je antiagregacijski učinak acetilsalicilne kiseline (ASK 100 mg/dan i 200 mg/dan) na trombocite 351 bolesnika sa solidnim tumorima. ASK produžuje vrijeme agregacije, pa je njen antiagregacijski učinak važan u prevenciji tromboze. Korišten je agregometar Siemens PFA-100 s kolagenskim/epinefrinskim uloškom. Prosječna dob bolesnika bila je 64,33 ± 11,67 godina. Muškaraca je bilo 74 (21,08%), a žena 277 (78,91%). Bolesnici su bolovali od tumora glave i vrata 34 (9,69%), dojke 222 (63,2%), pluća 4 (1,14%), trbuha 54 (15,4%), mokraćnog 4 (1,14%) i spolnog sustava 33 (9,4%). Vrijednosti agregacije >160 sekundi pokazuju djelovanje ASK na trombocite. Antiagregacijski učinak ASK 100 mg/dan bio je u 142 (40%) bolesnika, a nije ga bilo u 209 (60%). Prosječni antiagregacijski učinak ASK 100mg/dan za muškarce bio je 169,29 ± 79,54 sekundi, a za žene 168,51 ± 69,71 sekundi. Statistički značajne agregacijske razlike između rezultata muškaraca i žena nije bilo (p = 0,759). Interindividualna varijabilnost agregacije pokazuje koeficijent varijabilnosti CV = 41-47%. Iz skupine koja nije reagirala na ASK 100 mg/dan izdvojeno je 40 bolesnika i liječeno primjenom ASK 200 mg/dan. Reagiralo je 17 (42%), a nije 23 (58%). Nije bilo statistički značajne razlike dvaju mjerenja uzoraka 38 istih osoba, u razmaku od mjesec dana (p =

0,063), što pokazuje intraindividualnu stabilnost agregacije. S obzirom na to da se samo u 40% osoba uočava antiagregacijski učinak ASK 100 mg/dan i 200 mg/dan, preporučuje se individualno doziranje oslonjeno na agregacijski nalaz.

KLJUČNE RIJEČI: *tumori, agregacijska rezistencija, acetilsalicilna kiselina, agregometar PFA-100*

INTRODUCTION

Acetylsalicylic acid (ASA) has been a useful medicine for more than 110 years. It is best known in the management of headaches, rheumatism, inflammation, and in the prevention of thrombosis and tumors (1). In our parts, ASA is most commonly used in a dose of 100 mg/day. The question is whether ASA in this dose exerts the same antiaggregating effect on platelets of all humans and protects them from thrombosis? Studies show that 8-45% of the population are resistant to the anti-aggregating effect of ASA (2). There are different types of aggregometers and different principles of aggregation available. Some produce platelet aggregation in plasma, some in whole blood. In the absence of standard test method, the reported data of ASA resistance range from 5.5% to 60% (3-6).

MATERIAL AND METHODS

Blood samples were taken from 351 solid tumor patients consuming ASA 100 mg/day. The mean age of patients was 64.33 ± 11.67 years (Fig. 1). Among them, there were 74 (21.08%) male and 277 (78.91%) female patients (Fig. 2). The patients suffered from head and neck tumors - 34 pts (9.69%), breast cancer - 222 pts (63.2%), lung cancer - 4 pts (1.14%), abdominal cancer - 54 pts (15.4%), urinary cancer - 4 pts (1.14%), and genital tract cancer - 33 pts (9.4%) (Fig. 3). From this group, 40 patients resistant to ASA 100 mg/day were singled out and their daily dose was increased to 200 mg/day. To investigate the intraindividual stability of platelet aggregation, the test was carried out two times at a 1-month interval on the same 38 patients. Blood from the cubital vein was collected in 4.5mL glass vacutainer coagulation tubes using buffered sodium citrate 0.105 M (≈3.2%) as an anticoagulant. Platelet aggregation in whole blood was measured using the Siemens PFA-100 System (Platelet Function Analyser) with a collagen/EPI test cartridge. The cut-off value was 160 seconds. Values above 160 seconds were considered to be caused by the effects of ASA on platelet aggregation. Statistical analysis was performed using the Mann-Whitney Rank Sum Test and Wilcoxon Signed Rank Test to calculate mean values (mean), standard deviation (SD), coefficient of variation (CV), percentage (%) and probability (p).

RESULTS

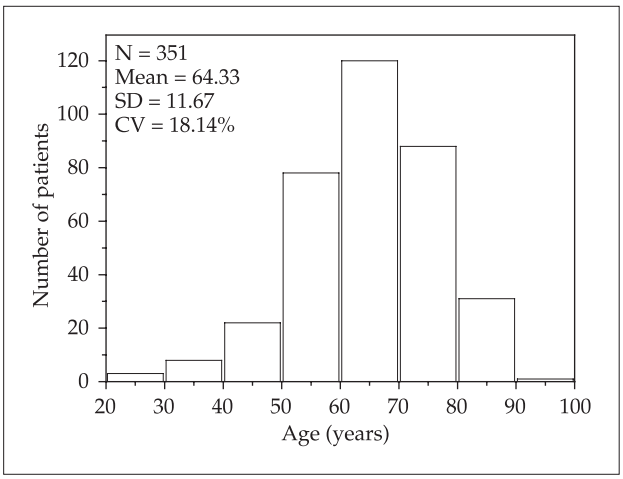

Figure 1. Age distribution of patients receiving ASA. The mean age of 351 patients is 64.33 ± 11.67 years. The coefficient of variation (CV) of age is 18.4%.

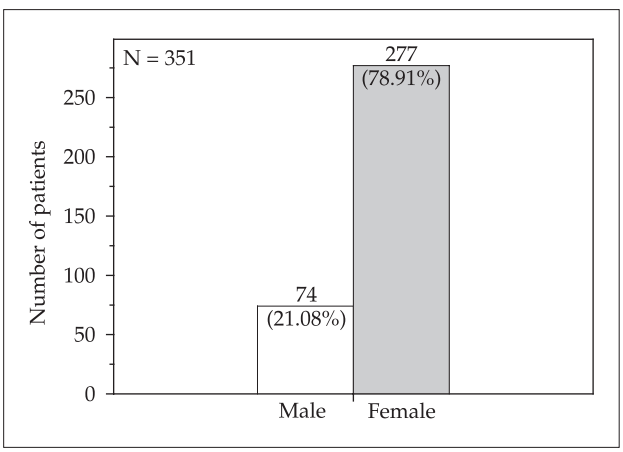

Figure 2. Gender respresentation. Males accounted for 21.08%, and females for 78.91% of the study population.

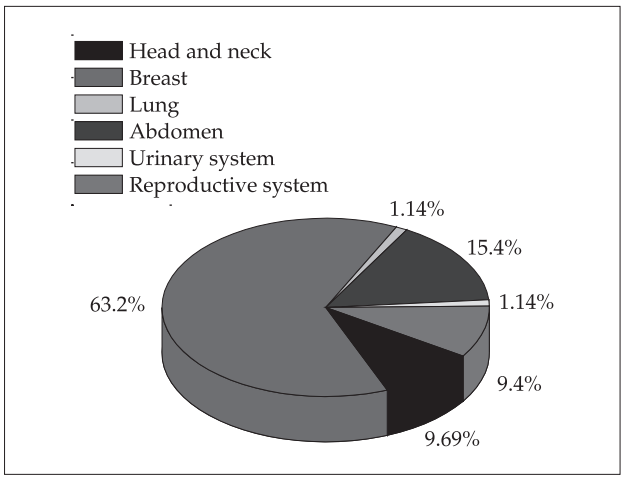

Figure 3. Representation of tumor sites. The most common site is the breast (63.2%), followed by the abdomen (15.4%), head and neck (9.69%), reproductive system (9.4%), lungs (1.14%), and urinary system (1.14%).

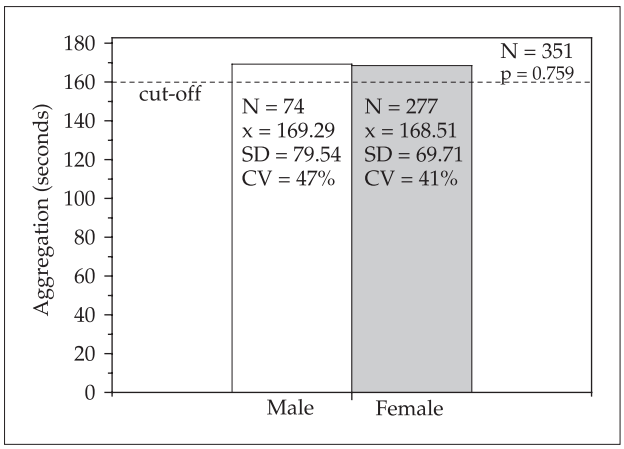

Figure 4. Gender-adjusted mean value of platelet aggregation levels. The relatively high coefficient of variation (CV), ranging from 41 to 47%, reveals a wide interindividual variation of platelet aggregation. There is no gender difference in the effects of ASA on platelet aggregation. Cut-off = 160 sec. Mann-Whitney Rank Sum Test T = 12960, (p = 0.759).

DISCUSSION

A comparison of platelet aggregation in male and female subjects showed no statistically significant difference between the two (p = 0.759, Figure 4). A wide interindividual variation in aggregation values was also found (CV 41-47%, Fig. 4). The anti-aggregating effect was not reported in 60% of the patients receiving ASA 100 mg/day (Fig. 5). A similar response pattern was seen in

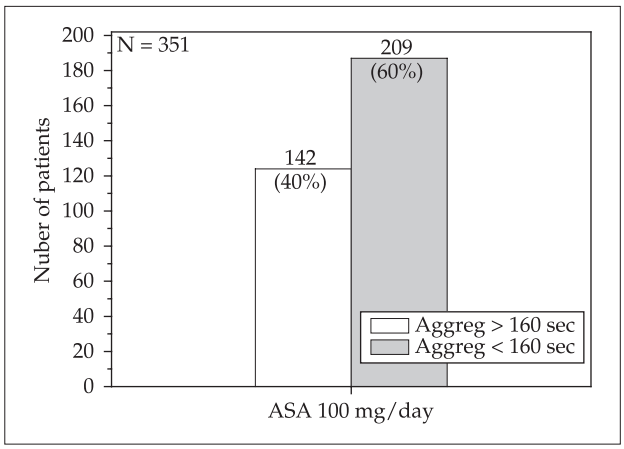

Figure 5. Values of platelet aggregation in 351 patients taking ASA 100 mg/day. The anti-aggregating effect was present in 142 (40%), and absent in 209 (60%) pts. Cut-off = 160 sec.

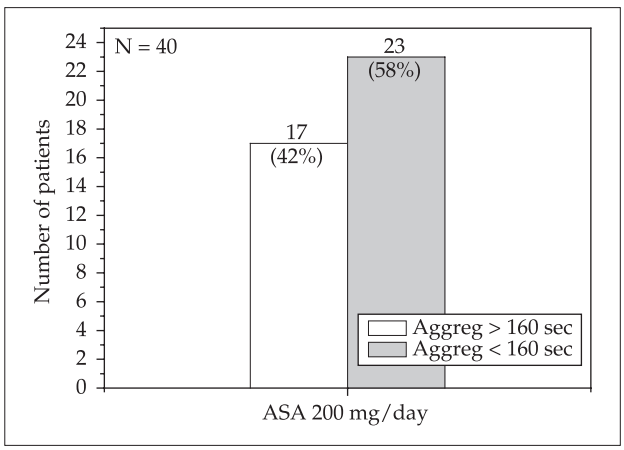

Figure 6. Values of platelet aggregation in 40 patients taking ASA 200 mg/day. After the patients not responding to ASA 100 mg/day had received ASA 200 mg/day, the anti-aggregating effect was present in 17 (42%), and absent in 23 (58%) pts. Cut-off = 160 sec.

ASA 100 mg/day-resistant patients after their dosage had been increased to 200 mg/day. They showed resistance of 58% (Fig. 6). The results are similar to those observed worldwide. Only for PFA-100 testing, 7 different cut-off values have been used around the world (7-13). In addition, aggregation has been demonstrated to depend on the type of test used. A comparison of the results obtained by the PFA-100 and light transmittance aggregometry (LTA) showed resistance up to 60% and 4%, respectively (14).

In the same 38 patients in whom aggregation was measured two times with a 1-month interval,

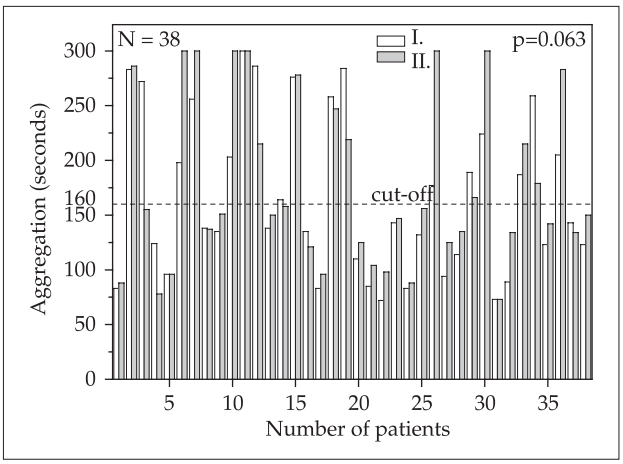

Figure 7. Intraindividual stability of platelet aggregation. Platelet aggregation of the same 38 patients was measured two times with a 1-month interval. Aggregation <160 seconds, in both measurements, remained under the cut-off line. Aggregation >160 seconds, in both measurements, remained above the cut-off line. There is no statistically significant difference between the first and second measurement. Wilcoxon Signed Rank Test W= 228, T+ = 429, T-= -201 (P = 0.063).

the intraindividual stability of the parameter was observed. The majority of patients whose aggregation values were under the cut-off line before and 1 month after mostly remained under the cut--off line. Likewise, those who were above the cut--off line mostly remained above this line, too. There was no statistically significant difference between the two measurements with a 1-month interval (p = 0.063).

Mechanisms that lead to different anti-aggregating effects of ASA have not been fully elucidated yet. Resistance to ASA may be due to the following: reduced accessibility of aspirin to receptor site due to concomitant intake of other NSAIDs (15), genetic polymorphism of enzymes like COX-1, COX-2 or thromboxane A2 synthase (16), increased reactivity of platelets towards other aggregating factors (17), increased rate of entry of new platelets into the circulation (18), alternate pathways of thromboxane synthesis (19), poor patient compliance (20). Overweight people and those with type 2 diabetes also show resistance to ASA (21).

CONCLUSION

This paper demonstrates ASA-resistance in 60% of solid tumor patients, which complies with data on other diseases reported in the literature. It also demonstrates a wide interindividual variability of aggregation with the coefficient of variation CV 41-47%. However, the intraindividual levels of aggregation are stable and not statistically significant (p = 0.063). No statistically significant difference in platelet aggregation between genders is shown (p = 0.759). Despite the development of ASA resistance, ASA treatment is considered a useful therapeutic tool. Long-term aspirin administration in patients at high risk of occlusive vascular events reduced up to 34% of nonfatal myocardial infarction, 25% of nonfatal stroke, and 18% of all-cause mortality (22). The dose should be adjusted according to the individual results of the platelet aggregation test.

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