

# The Association of Antiplatelet Aggregation Effect of Aspirin and Platelet Count. Possible Dosage Implications

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## SUMMARY

### Background

El 30% de los pacientes presentan antiagregación plaquetaria inadecuada con 100 mg/día de aspirina (AAS) luego de la cirugía de revascularización miocárdica (CRM), que podría deberse a una acción inhibitoria menor de esta dosificación de AAS a la mayor activación plaquetaria y al aumento del recambio plaquetario que ocurren en el posoperatorio.

### Objetivos

Evaluar la relación entre el recuento plaquetario y el menor efecto antiagregante y determinar si dosis fragmentadas de AAS mejoran la antiagregación.

### Material y métodos

Luego de la CRM con bypass cardiopulmonar (2,95 bypass en promedio), se aleatorizaron prospectivamente 50 pacientes a tres grupos: 18 pacientes (G100) a 100 mg/día, 14 (G300) a 300 mg/día y 18 (G100×3) a 100 mg 3 veces por día de AAS. En el preoperatorio todos recibieron 100 mg/día. La reactividad plaquetaria se midió mediante agregación en sangre entera con ácido araquidónico antes de la cirugía (T0), al primero (T1), tercero (T2) y séptimo días (T3) y al mes (T4) pos-CRM.

### Resultados

En el preoperatorio todos los pacientes tenían valores óptimos de antiagregación (0 Ω). En el posoperatorio, los pacientes del G100×3 tuvieron mejores niveles de antiagregación (p < 0,05). Ningún paciente del G100×3 tuvo valores ≥ 6 Ω, correspondientes a los de personas sanas sin AAS, a diferencia de 5 pacientes (28%) del G100 y 4 pacientes (29%) del G300. Se observó una asociación estadísticamente significativa entre la antiagregación plaquetaria y el recambio del número de plaquetas (R2 = 0,57; p = 0,001). Un recambio diario > 20% se relacionó con valores de agregación plaquetaria ≥ 6 Ω con un OR = 2,1 (IC 1,8-4,21; p = 0,0028).

### Conclusiones

En los pacientes sometidos a CRM, la menor respuesta antiagregante a la AAS se correlacionó con el recambio aumentado de plaquetas. El tratamiento podría fragmentarse con dosis bajas de AAS para obtener mejor antiagregación.

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## Key words >

Aspirina - Antiagregantes plaquetarios - Plaquetas - Inflamación - Interleucina 6 - Revascularización miocárdica

## Abbreviations >

<b>AA</b>	Arachidonic acid	<b>WBPA</b>	Whole-blood platelet aggregation
<b>ASA</b>	Acetylsalicylic acid (aspirin)	<b>Ω</b>	Ohm
<b>NSAIDs</b>	Nonsteroidal anti-inflammatory drugs	<b>IL-6</b>	Interleukin-6
<b>CPB</b>	Cardiopulmonary bypass	<b>IQR</b>	Interquartile range
<b>COX-1</b>	Cyclooxygenase-1	<b>TNF-α</b>	Tumor necrosis factor alpha
<b>COX-2</b>	Cyclooxygenase-2	<b>TXA2</b>	Thromboxane A2
<b>CABGS</b>	Coronary artery bypass-graft surgery		

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## BACKGROUND

Around 30% of patients present suboptimal platelet inhibition with aspirin (ASA) during the first week after coronary artery bypass-graft surgery (CABGS), (1, 2), which is associated to increased risk for occlusion of coronary bridges and increased mortality. (3, 4)

After CABGS, ASA is usually given as a daily dose of 75 to 325 mg. (5) Despite this drug has a half-life of 13 to 19 minutes, (6) it achieves a permanent inhibition of the cyclooxygenase-1 enzyme (COX-1) at platelet level; if this is associated to the fact that platelets are cells with no nucleus, unable to regenerate COX, it causes the production of thromboxane (TXA2) stay almost exclusively related to the production of new platelets. (7)

Increased platelet production (increased platelet turnover) during the first week after surgery is due to the thrombopoietic stimulus caused by inflammatory cytokines. (8-10) This platelet increase is one of the mechanisms proposed as being the cause of "resistance to ASA". (2, 6, 11)

This pilot study was designed to assess the relation between increased platelet turnover during the first week after CABGS and reduced antiaggregation effect with ASA. Another objective was to determine if dividing the dose of ASA in 100 mg 3 times a day would improve antiaggregation levels compared with a once-daily dosing of 100 or 300 mg.

## MATERIAL AND METHODS

A prospective, randomized, single-center study was designed, which included patients undergoing isolated elective CABGS, with cardiopulmonary bypass (CPB).

We enrolled patients over 18 years of age, with no contraindications to ASA therapy, no concomitant treatment with clopidogrel or oral anticoagulation, and no previous intake of other nonsteroidal anti-inflammatory drugs (NSAIDs). Pregnant women and patients with creatinine clearance  $\leq 30$  ml/min were excluded.

The study was conducted following the Declaration of Helsinki, and approved by the Ethics Committee of the institution (FLENI), and reported to the regulatory institution of the country (ANMAT). An ad hoc database was performed to anonymously include the data of all the patients by a numeric code.

Until the day of the CABGS, all the patients were treated with ASA 100 mg/day, and then were randomized –by sealed envelope– when entering the Cardiovascular Recovery Unit after surgery.

Dosage of interleukin 6 (IL-6) and platelet count was performed, and platelet aggregation was measured 24 hours before the CABGS (T0), and at 24 hours (T1), 3 days (T2), 7 days (T3), and 1 month (T4) after surgery.

T0 represents values of platelet aggregation with 100 mg/day of ASA during post surgery; T1 shows the possible effects of CPB and surgery. Samples obtained in T3 correspond to the post surgery week, period in which analyses are most vulnerable to altered response to ASA action, and there is higher risk for occlusion of coronary bridges. (1, 4, 9)

Blood was obtained by antecubital venepuncture between 6:00 and 8:00 hours (prior to ASA dose); it was stored in tubes containing sodium citrate, and centrifuged

at 160xg for 15 minutes. Platelet aggregation was measured within 2 hours by whole-blood impedance (CHRONO-LOG 590D) using arachidonic acid (AA) 0.5 mM/L as agonist, and it was expressed in ohms ( $\Omega$ ).

Platelet values were expressed as  $n/mm^3$  and IL-6 levels were dosed by ELISA and expressed in pg/ml.

Daily platelet turnover was defined as the percentage of change in the platelet count divided by the number of days between the two determinations.

To set a cut-off point to allow the definition of values of platelet aggregation without aspirin, platelet aggregation was determined with the same method in 50 samples of 30 controls which were not treated with aspirin.

## Statistical Analysis

Continuous variables with abnormal distribution were expressed as mean and interquartile ranges, and were compared to Wilcoxon signed-rank test (among subjects) and Kruskal-Wallis and Wilcoxon rank sum test (among groups). Variables with normal distribution were expressed as mean  $\pm$  standard deviation, and were compared to the t test.

Categorical variables were expressed as frequency and percentages, and compared to the chi-square test and the Fisher's exact test, as appropriate.

For multiple comparisons of three groups, ANOVA was used together with Bonferroni and Sidak test.

Spearman correlation coefficient was used, and significance of p and square R were analyzed. A p value  $< 0.05$  was considered significant. STATA 9.0 was used for the analysis.

## Intervention

Prior to CABGS, patients will receive ASA 100 mg/day at least during the week before surgery, with no concomitant treatment with other antiplatelet drug or NSAID. On admission to Cardiovascular Recovery, patients were randomly assigned to three groups: G100, who were treated with ASA 100 mg/day on once-daily dosing, G300, 300 mg/day on once-daily dosing, and G100 $\times$ 3, who received 100 mg every 8 hours. The use of NSAIDs or other antithrombotic drugs was not allowed, except for doses of heparin as prophylaxis for deep vein thrombosis. Acetaminophen and morphine derivatives were used to treat pain.

The ASA single dose was administered in the morning, as the first dose of G100 $\times$ 3.

## RESULTS

Eighty patients were selected; 8 patients were excluded because CABGS was performed without CPB, 7 were also excluded due to requiring anticoagulation therapy in the perioperative period, 1 because of concomitant treatment with clopidogrel, and 2 because of chronic NSAID requirement. A patient died during surgery, and 5 were excluded due to operational issues that hampered lab tests on the days defined by the protocol. One patient was excluded because he was not administered ASA the week before surgery, and 5 did not provide their consent to participate (Figure 1).

Finally, 50 patients were randomized: 18 to G100, 14 to G300, and 18 to G100 $\times$ 3.

Table 1 shows population characteristics, concomitant treatment, and surgery data. Mean age was  $64.9 \pm 9$  years; 94% were men, and no significant differences were observed among the three groups

in the prevalence of high blood pressure, diabetes, or smoking. A 14% of the overall population had a history of coronary angioplasty, and one patient had undergone previous coronary artery bypass surgery. There were no differences among groups regarding prior treatment.

Patients had an average of  $2.95 \pm 0.65$  coronary bridges ( $2.94 \pm 0.64$ ,  $3.1 \pm 0.6$  and  $2.77 \pm 0.7$  in G100, G100×3 and G300, respectively; ANOVA = 0.8). CPB and aortic clamping time took 76 minutes (IQR 64-91) and 44 minutes (IQR 37-52), with no differences among groups.

None of the patients died during the study period. Three patients—two from G100 and one from G100×3—required surgery to be repeated due to bleeding.

### Interleukin-6

IL-6 levels showed a peak at T1, with a progressive reduction until reaching similar levels to those before surgery (T0) in the sample of the month after surgery (T4) (Figure 2 and Table 2).

No statistically significant differences were observed among the groups in none of the periods analyzed.

Platelet count showed an initial reduction at T2, with a substantial increase at T3 (Figure 3). On average, there was a 50% increase (IQR 39.5-65.5%) between T2 and T3, with no significant differences among the three groups [53% (IQR 39-66) in the G100, 47.5% (IQR 30-69) in the G300, and 61% (IQR 41-69) in the G100×3; ANOVA  $p = 0.87$ ] (Table 3).

All patients showed optimal levels of platelet antiaggregation at T0 (0  $\Omega$ ). At T2, 11 patients (61%) from G100, 3 (21%) from G300 and 1 (5%) from G100×3 presented with values  $> 0 \Omega$ . At T3, 11 patients (61%) from G100, 7 (50%) from G300 and 5 (27%) from G100×3 presented with platelet

aggregation values  $> 0 \Omega$  ( $p = 0.154$  for G100 vs. G300;  $p = 0.05$  for G100×3 vs. G300;  $p = 0.044$  for G100×3 vs. G100).

Control group without ASA therapy showed a whole-blood platelet aggregation value with AA of 6  $\Omega$  (IQR 3-10  $\Omega$ ). None of the patients from G100×3 showed this platelet aggregation value, as opposed to 5 patients (28%) from G100 and 4 (29%) from G100 between T2 and T3.

There was a correlation between platelet count and platelet aggregation ( $p$  of correlation  $< 0.0001$ , square  $R = 0.57$ ) (Figure 4). It was observed that the higher the platelet turnover the lower the ASA antiaggregation effect; a daily turnover  $> 20\%$  was associated with risk for platelet aggregation  $\geq 6 \Omega$  with OR 2.14 (CI 1.08-4.21;  $p = 0.0028$ ).

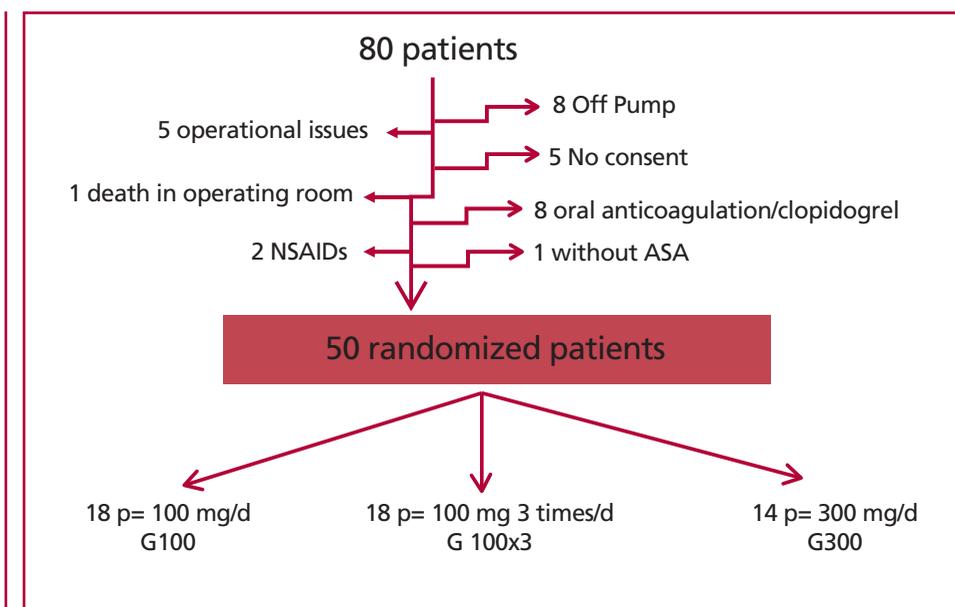
### DISCUSSION

Our study showed a correlation between increased platelet turnover which occurred after CABGS and reduced ASA antiaggregation effect. Despite optimal platelet antiaggregation levels with a single dose of 100 mg/day before surgery, more than 50% of the two groups who continued with a single daily dose lost these optimal antiaggregation levels after surgery, as opposed to a 27% of the group treated with divided doses throughout the day (a statistically significant difference).

Even more important is that 28% and 29% of the patients in G100 and G300, respectively, had the same or higher platelet aggregation levels than those of healthy subjects with no ASA therapy. However, none of the G100×3 patients showed these platelet aggregation values.

Particularly at the early stage of CABGS postoperative period, a high rate of “aspirin resistance” has been reported, which affects nearly 30% of the

Fig. 1. Patient selection and randomization.



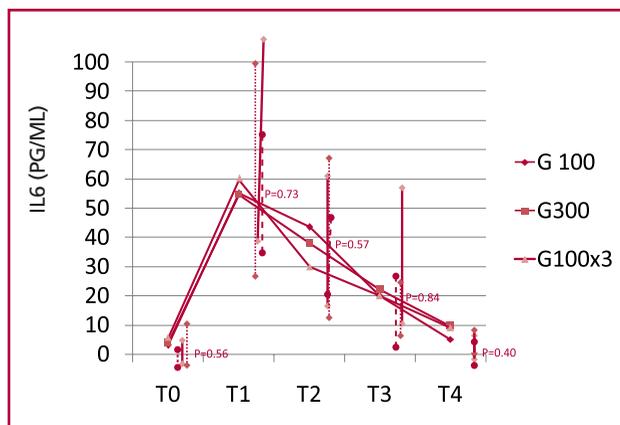
	Global	100	100x3	300	p 100 vs. 200 100 vs. 300
Age	64.9 ± 9	64.1 ± 4	64.2 ± 9	64.3 ± 5	ns
HBP	34 (69)	13 (72)	12 (71)	9 (64)	0.99 0.95
DM	11 (22)	4 (22)	4 (23)	3 (21)	0.9
SMK	11 (22)	6 (33)	3 (18)	2 (14)	0.54 0.75
Ex SMK	23 (47)	8 (44)	11 (65)	4 (29)	0.62 0.51
PTCA	7 (14)	1 (6)	4 (24)	2 (14)	0.94 0.99
CABGS	1 (2)	1 (6)			
Statins	33 (67)	11 (61)	14 (82)	8 (57)	0.5 0.9
ACE inhibitor	21 (43)	11 (61)	6 (35)	4 (29)	0.38 0.19
n Bridges	2.95 ± 0,65	2.94 ± 0.64	3.1 ± 0.6	2.77 ± 0,7	0.82 0.85
CPB	76 (64-91)	76 (64-88)	77 (68-91)	69.5 (54-93)	0.8 0.95
Clamping time	44 (37-52)	43 (39-51)	49 (42-55)	38.5 (30-47)	0.56 0.91

**Table 1.** Population and procedural characteristics

HBP: High blood pressure. DM: Diabetes mellitus. SMK: Smoking. PTCA: Transluminal coronary angioplasty. CABGS: Coronary artery bypass-graft surgery. ACE inhibitor: Angiotensin-converting enzyme inhibitor. CPB: Cardiopulmonary bypass.

**Table 2.** Levels of IL-6 per group from T0 to T4

	T0	T1	T2	T3	T4
G100	3	55	43.5	20	5
G300	4	54.5	38	22	9.5
G100x3	5.5	59.5	30	20	9

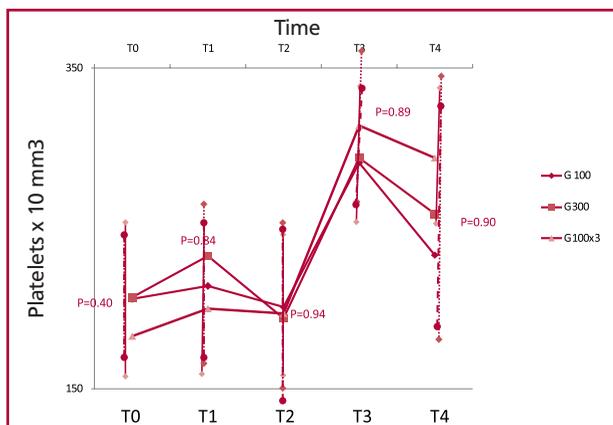


**Fig. 2.** Levels of IL-6. The levels of IL-6 reached their highest value at T1. There were no differences among the three groups.

**Table 3.** Platelet turnover at T2-T3 per group

G100x3	G100	G300
61% (41-69)	53% (39-66)	47.5% (30-69)

ANOVA = 0.78. G100x3: Group of patients with 100 mg of ASA every 8 hours. G100: Group of patients with 100 mg/day of ASA. G300: Group of patients with 300 mg/day of ASA.



**Fig. 3.** Platelet turnover. An initial reduction of platelet turnover (T2) with substantial increase at T3.

patients. (2, 12) There are multiple, pharmacokinetic and pharmacodynamic factors that influence in the lower antiaggregation response to ASA during perioperative period. (4, 13) One of the probable mechanisms is the increased platelet turnover that occurs in different clinical scenarios, such as coronary heart disease, diabetes, and cardiac surgery. (2, 6, 9, 17)

ASA acts by irreversibly inhibiting the COX-1, the enzyme that catalyzes the conversion of the arachidonic acid (AA) in the thromboxane A<sub>2</sub> (TXA<sub>2</sub>), which is antagonist for platelet aggregation. (18, 19) Because platelets have no nucleus, they are unable to regenerate COX, so TXA<sub>2</sub> synthesis depends on the biosynthesis of new platelets, and this usually occurs at a 10% rate per day. The irreversible action of the enzyme, together with the slow recovery of the number of platelets, explains the intense inhibition effect that is obtained with low daily doses of ASA. (20, 21)

The inflammatory process associated with CABGS with CPB, which is reflected by the increased inflammatory markers in blood, is connected with greater platelet activation and increased platelet turnover. (12, 22) Inflammatory cytokines, such as IL-6, IL-11, and TNF- $\alpha$ , directly or indirectly play a key role in thrombopoiesis, through production of thrombopoietin. (8, 10) The increased levels of thrombopoietin occur early after a surgery and reach their peak on day 3. Afterwards, it takes 2-3 days to reach the highest platelet turnover. (8) Despite no dosage of thrombopoietin was performed, reports match the results observed in our study, in which the peak of IL-6 took place on the first day after surgery, and the highest platelet turnover occurred on day 7.

To obtain an effective platelet antiaggregation, it is necessary to block at least 10% of the TXA<sub>2</sub> production, which may be achieved with low ASA doses. (19, 23) The half-life of aspirin is 20 minutes (19, 23), so when the circadian rhythm of platelet production is increased, regardless of the dose used, the entry of new platelets into the circulation after 20-30 minutes exposes unblocked COX-1 and able to produce TXA<sub>2</sub>. In our study, we observed better

platelet antiaggregation values with divided doses of aspirin throughout the day, which provides re-exposure of new circulating platelets to the inhibitory action over COX-1; this avoids TXA<sub>2</sub> interdosage, which occurs when it is administered every 24 hours (Figure 5).

Previous studies assessed the use of divided doses, but of 325 and 600 mg twice or three times a day, with dissimilar outcomes. (9) It may be due to the fact that higher ASA levels inhibit TXA<sub>2</sub> production at platelet level, but also the prostacyclin production with antiaggregation and vasodilating effect at endothelial level. (19) Using lower doses could prevent this imbalance and thus stimulate aspirin antiplatelet action.

Other mechanisms of platelet activation which cannot be measured with this technique, (24) as well as the lower response of new cross-linked platelets, secondary to lower action over the COX-1, and also to TXA<sub>2</sub> formation through COX-2 present in these cells, were not evaluated and may also explain the low response to antiaggregation in processes with thrombocytosis. (25)

#### Clinical implications in other areas in cardiology

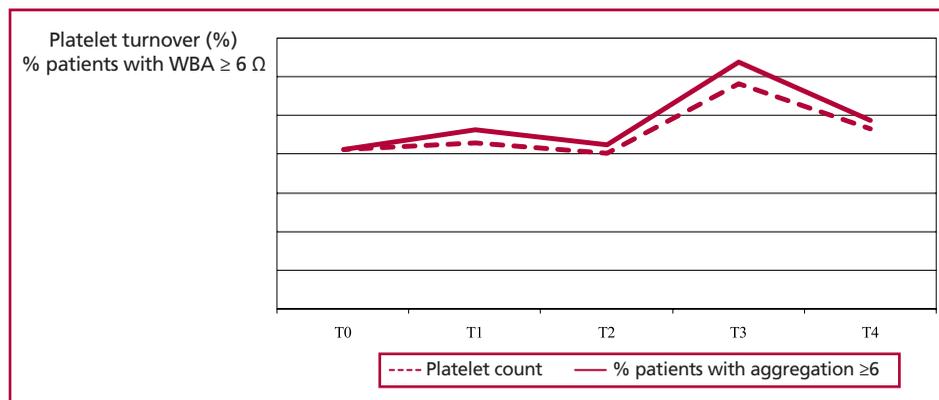
The CABGS with CPB is a model of inflammation and augmentation of platelet turnover; however, with different gradients, these data may be applied to other clinical scenarios which refer inflammatory response, increased platelet turnover, and resistance to antiaggregation agents, as is the case of acute coronary syndrome and coronary angioplasty.

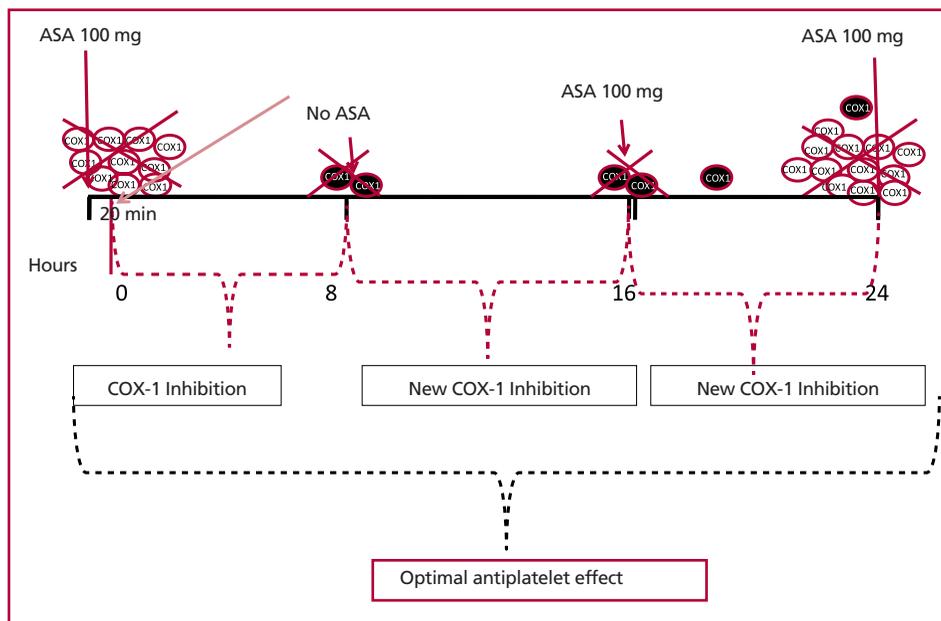
#### Limitations

This is a study with a low number of patients, but it was designed as a pilot study. Larger studies are required to confirm outcomes and assess the clinical impact of this variation in levels of platelet antiaggregation on a large scale.

Because this study was carried out in a single center, it is methodologically inappropriate to extrapolate its data; nonetheless, since a standard surgical strategy was used, no factors should influence the analyzed variables.

**Fig. 4.** Relation between platelet turnover and platelet aggregation. A high correlation between platelet turnover variation and platelet aggregation levels was observed. The higher the platelet turnover, the higher the platelet aggregation levels. WBPA: Whole-blood platelet aggregation.





**Fig. 5.** Antiaggregation effect of divided doses of ASA. A divided low dose of aspirin inhibits COX-1 occurrence, which is present in new platelets when turnover is increased.

An only platelet aggregation technique for measuring was used. Several methodologies were described, and some of them are complementary. However, the one used in this study is currently considered the pattern method. (26)

## CONCLUSIONS

Variation in antiplatelet effect of ASA after CABGS is associated with platelet turnover. An increased turnover, higher than 20% per day, doubles the risk for having –on the seventh day of the CABGS– platelet aggregation values equal to those of a group who were not administered aspirin.

Low dose of ASA (100 mg every 8 hours) was better to prevent variations in antiaggregation levels, and prevented patients from reaching same or higher aggregation values than those of the group who did not receive ASA.

## RESUMEN

**Relación entre el efecto antiagregante de la aspirina y el recuento plaquetario. Posibles implicaciones en la dosificación**

### Introducción

El 30% de los pacientes presentan antiagregación plaquetaria inadecuada con 100 mg/día de aspirina (AAS) luego de la cirugía de revascularización miocárdica (CRM), que podría deberse a una acción inhibitoria menor de esta dosificación de AAS a la mayor activación plaquetaria y al aumento del recambio plaquetario que ocurren en el posoperatorio.

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tres grupos: 18 pacientes (G100) a 100 mg/día, 14 (G300) a 300 mg/día y 18 (G100×3) a 100 mg 3 veces por día de AAS. En el preoperatorio todos recibieron 100 mg/día. La reactividad plaquetaria se midió mediante agregación en sangre entera con ácido araquidónico antes de la cirugía (T0), al primero (T1), tercero (T2) y séptimo días (T3) y al mes (T4) pos-CRM.

## Resultados

En el preoperatorio todos los pacientes tenían valores óptimos de antiagregación (0 W). En el posoperatorio, los pacientes del G100×3 tuvieron mejores niveles de antiagregación ( $p < 0,05$ ). Ningún paciente del G100×3 tuvo valores  $\geq 6$  W, correspondientes a los de personas sanas sin AAS, a diferencia de 5 pacientes (28%) del G100 y 4 pacientes (29%) del G300. Se observó una asociación estadísticamente significativa entre la antiagregación plaquetaria y el recambio del número de plaquetas ( $R^2 = 0,57$ ;  $p = 0,001$ ). Un recambio diario  $> 20\%$  se relacionó con valores de agregación plaquetaria  $\geq 6$  W con un OR = 2,1 (IC 1,8-4,21;  $p = 0,0028$ ).

## Conclusiones

En los pacientes sometidos a CRM, la menor respuesta antiagregante a la AAS se correlacionó con el recambio aumentado de plaquetas. El tratamiento podría fragmentarse con dosis bajas de AAS para obtener mejor antiagregación.

**Palabras clave** > Aspirina - Antiagregantes plaquetarios - Plaquetas - Inflamación - Interleucina 6 - Revascularización miocárdica

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#### Declaration of conflict of interest

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