Aspirin Resistance in Patients Undergoing Coronary Artery Bypass Grafting

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Abstract

Objective: Aspirin is a very common drug used after coronary artery bypass grafting. Significantly it is known to reduce mortality and the rate of ischemic complications after CABG. Resistance to Aspirin is a well known entity and has a great influence on clinical outcome. Our study will investigate the phenomenon of aspirin resistance in our patients that underwent coronary artery bypass surgery.

Methods: In a prospective controlled study 100 patients undergoing coronary artery bypass grafting (CABG) were included to investigate their sensitivity to Aspirin using platelets aggregometry study. Patients were followed up after one year to show their clinical outcome.

Results: 25 patients (25%) showed normal reaction to Aspirin (sensitive to treatment). 24 patients (24%) were preoperatively resistance to Aspirin and 51 patients (51%) developed this resistance postoperatively. The use of cardiopulmonary bypass, pump time and type of procedure showed no influence on the resistance rate. The one year follow up showed 5 deaths in the group of patients that developed the resistance preoperatively whereas resistance disappeared completely after one year in the perioperative resistant group.

Conclusions: Aspirin resistance occurs in a large portion of patients that undergo open heart surgery for coronary artery bypass grafting. It doesn't appear to last permanently but rather for a brief period. The worse outcome for patients with Aspirin resistance could be assumpted by the increase mortality in this group.

Keywords: Aspirin, CABG, Resistance.

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Introduction

Aspirin is a well known drug for its antithrombotic activity[(1)]. It is used as secondary prophylaxis in coronary artery disease management. Up to 17% of the patients received aspirin showed reduction in the vascular mortality which is shown in a recent meta analysis of placebo controlled trial[(2)]. In long term follow up 10-20% of patients experienced recurrent thrombotic events regardless of aspirin therapy[(3)].

The expected antiplatelets effect of aspirin is not always achieved where this could be explained by the inability to prevent the formation of thrombaxane (Tx) A2 due to failure of inhibition of platelets cyclooxygenase-(COX -) 1[(4)].

In patients with cardiovascular disease the

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incidence of aspirin resistance range from 5-40% where figures differ according to patient's cohort and assay method[5].
It was obvious that survival rate and graft patency is so much improved if aspirin is given in the early post operative period in patients undergoing coronary artery bypass grafting[6, 7].

Recently the influence of aspirin resistance in patients undergoing CABG gained wide interest as the normal response to aspirin therapy proved to cause 68% reduction in overall mortality and similar reductions in the rates of ischemic complications[8]. Off pump procedures seems to have low incidednce of resistance in comparison to that using cariopulmonary bypass[9, 10].
In this study we will investigate the aspirin resistance after CABG using various surgical procedures. Patients will be followed up after one year to show their clinical outcome.

Material and Methods
Blood samples (Citrated) were collected before surgery and on the 1, 3, 5 and 9 post operative dates. 10 healthy volunteers (not taking aspirin) were used as controls. Major cardiovascular and neurological events were obtained after one year period by asking the general physicians and patients through the phone call. Platelet aggregometry induced by arachidonic acid was used to retest patients initially identified as aspirin resistant before 12 months. Paracetamol or opiates are the only drugs used for analgesia.

Anticoagulation
As a protocol, all patients were kept on 100 mg oral Acetylsalicylic acid (ASA) preoperatively. Some patients discontinued ASA therapy five days prior to surgery according to their general physicians advice, resulting in 76 patients on and 24 patients without ASA treatment at the time of surgery.

All patients received 500 mg ASA intravenously postoperatively, followed by an oral dose of 100 mg once daily. Low molecular weight Heparin was given to all patients on prophylactic basis until transfer to the ward. A combined procedure with valve replacement or the presence of atrial fibrillation are some cases where additional anticoagulation was needed, heparin administration was maintained until coumadin therapy was therapeutic.

Platelets count Device
After centrifusion of the plasma in order to get platelets rich plasma, the blood of every patient is tested for its platelets count before examining the aggregation profile.

Platelet aggregometry
Citrated blood samples were centrifuged at 150 rpm for 15 minutes to obtain platelet rich plasma, followed by a second centrifugation (1500 rpm, 15 minutes) for obtaining the platelet poor plasma (used as blank value). The PAP-4 moeLab™, Berlin Germany(four-channel aggregometer) was used to measure the Platelet aggregation using the turbidimetric method according to the manufacturers instructions. The principle of this method depends on platelets that are stirred and light transmission is measured. Upon activation platelets start to form pseudopodia thereby transiently reducing light transmission thereafter, platelets aggregate and move to the bottom of the cuvatte this allowing higher light transmission. By measuring the transmitted light this process of platelets aggregation can be monitored.

After preincubation for 5 minutes at 37° C, platelets were stimulated by addition of 1 mM arachidonic acid (ARA). In vitro addition of ARA to normal platelets rich plasma results in a burst of oxygen consumption, thromboxane formation and platelets aggregation. Aggregation exceeding the 30% threshold indicates that platelets were not sufficiently suppressed. To evaluate if platelets exhibited

resistance or not the test was repeated after in vivo addition of ASA reaching concentration of 10µM and 25µM.

Patient was defined to have aspirin resistant if platelet aggregation exceeded the threshold of 30% despite in-vitro addition of 25µM Aspisol to exclude non-compliance.

Results

As shown in Table (1), 76% of patients were on aspirin upon admission. 85% were operated using cardiopolmonary bypass circulation. Combined procedures were performed in 35%. The majority of patients who used the cardiopolmonary bypass (83%) didn't exceed 120 minutes as pump time.

Table 1. Patient characteristics

	Yes	No
off-pump	15 (15%)	85 (85%)
Pump time>120 min	17 (17%)	83 (83%)
combined procedures	35 (35%)	65 (65%)
Preoperative Aspirin	76 (76%)	24 (24%)
preoperative Clopidogrel	6 (6%)	94 (94%)

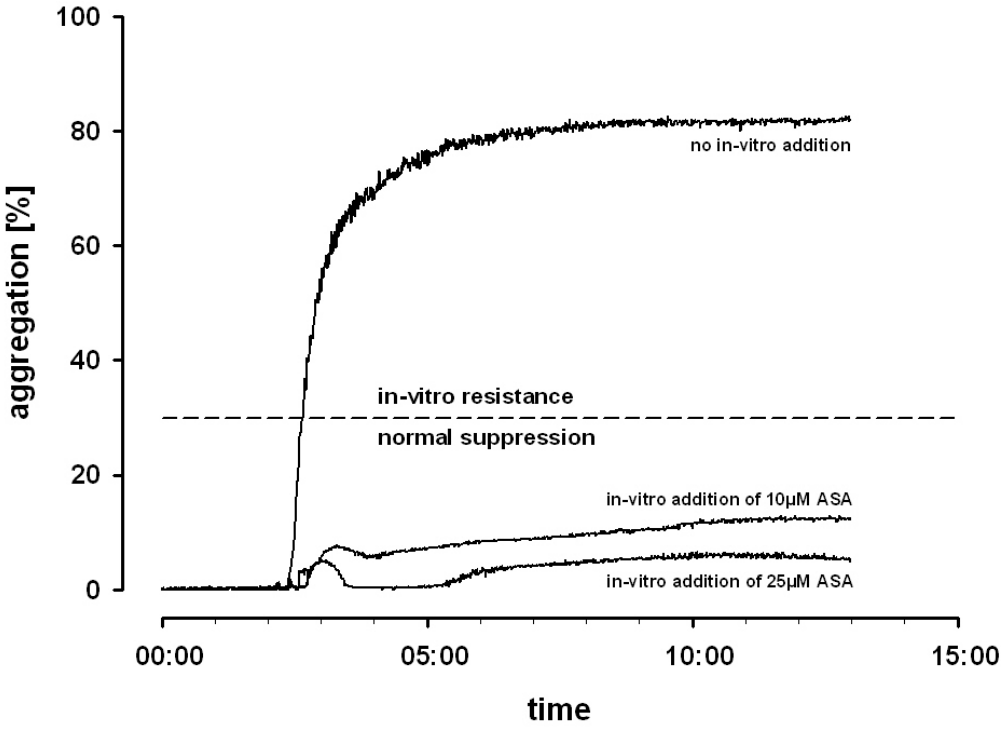

Figure 1. Arachidonic acid induced aggregation in healthy volunteers (controls without Aspirin)

Aspirin response and platelet levels

Volunteers used as controls and not taking aspirin showed platelet aggregation of 83% after stimulation with ARA, which was inhibited totally by in-vitro addition of 10µM and 25µM ASA to the platelet rich plasma

(Figure 1). It was only 22% of all patients that showed a typical inhibitory reaction towards aspirin treatment which is revealed by suppression of platelet aggregation below the 30%-threshold in the arachidonic acid induced aggregometry. The inhibition of ARA-induced aggregation was almost complete and could not be influenced by further in-vitro addition of aspirin in patients that showed typical response to oral aspirin (Figure 2). The platelet count dropped significantly during the first 3 post operative dates and started to rise again in the 5th day reaching the base line value and even exceeding that by the 9th day as shown in Figure (3).

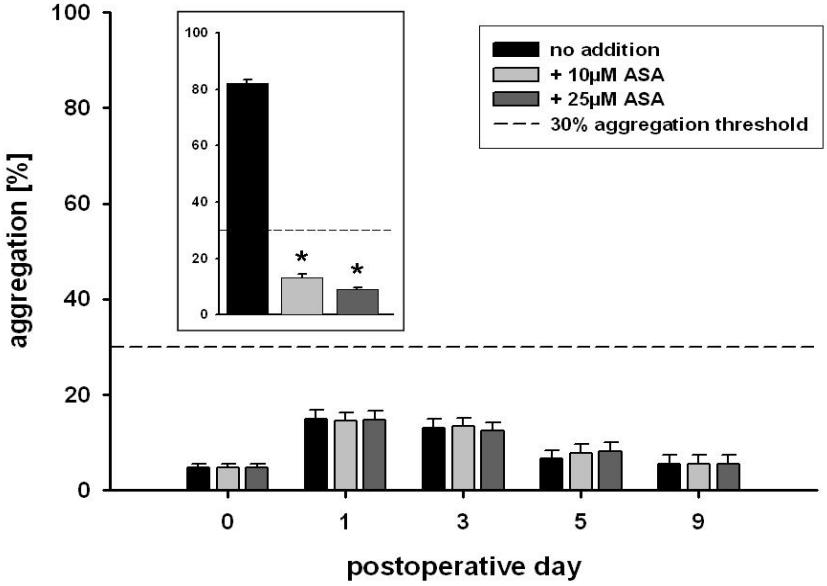

Figure 2. Arachidonic acid induced aggregation in normal reacting patients on aspirin (n=25); Insert: healthy volunteers not on aspirin, * p<0.05 vs. without in-vitro ASA-addition

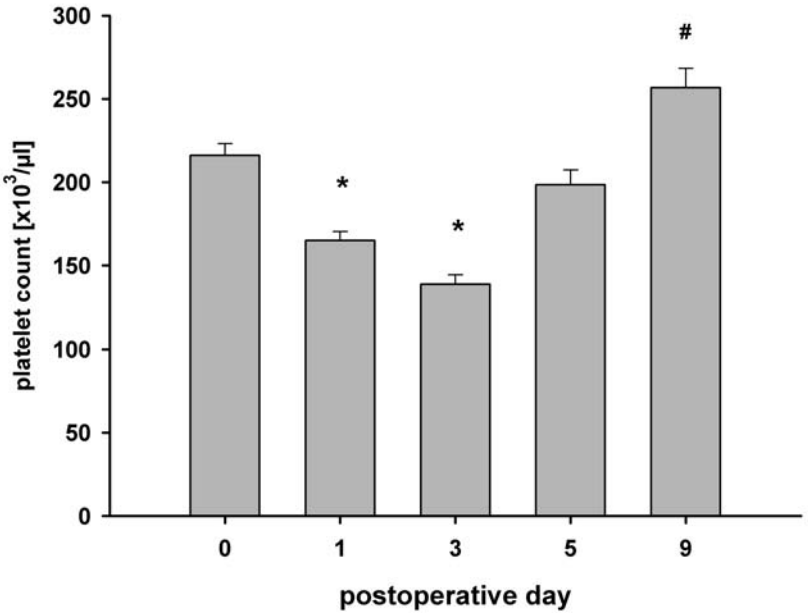

Figure 3. Platelet count (n=100), * p<0.05 vs. before surgery (day 0), # p<0.05 vs. day 0

Aspirin resistance in the preoperative period

Obviously some patients were aspirin resistant preceding surgery – exceeding the 30%-aggregation threshold. Figure (4) shows the course of the preoperatively resistant patients which compromise 27 patients out of the 100 studied. In view of the fact that failure of suppressed ARA-induced aggregation could imply that patients had a pharmacokinetic resistance or did not take their aspirin, we furthermore tested whether in-vitro addition of aspirin to the platelets would inhibit the ARA-response. Nevertheless and even after in vitro addition of above physiological concentrations of ASA (25µM), platelet aggregation remained higher than the threshold of 30%. In comparison to preoperative values ASA therapy following surgery reduced platelet aggregation in these patients appreciably but aspirin resistance was still present since aggregation values stayed over the 30%-threshold.

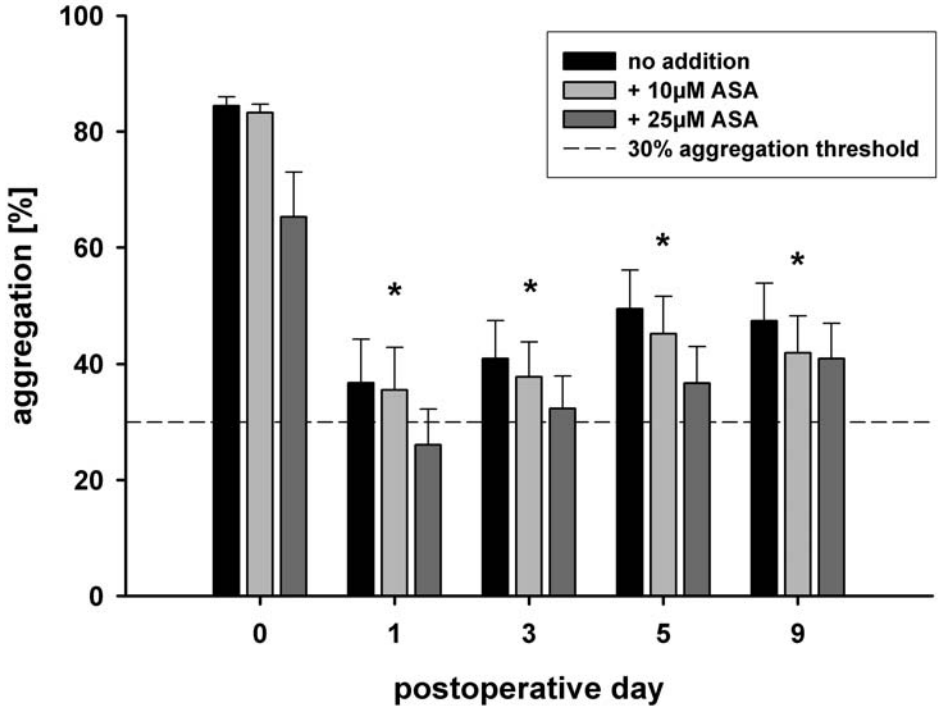

Figure 4. Arachidonic acid induced aggregation in preoperativelyresistant patients (n=24)
*** p<0.05 vs. before surgery (day 0)**

Table 2. Postoperative resistant patients

	nonresistant	resistant	p
off-pump	7	8	n.s.
on-pump	45	40	n.s.
pump-time >120 min	8	11	n.s.
pump-time <120 min	35	31	n.s.
combined procedures	15	20	n.s.
Isolated CABG	34	31	n.s.

Prior to surgery 76 patients (76%) were on oral aspirin. In this group 11 showed preoperative aspirin resistance. It was clear that the rate of preoperative resistance was significantly

higher (88%) in patients that didn't take aspirin before surgery, despite testing after in-vitro addition of ASA, representing pharmacokinetic ASA resistance. The association between the rate of preoperative aspirin resistance and negative ASA treatment previous to surgery was statistically significant ($p<0.0001$).

Aspirin resistance in the post operative period

Nearly half of all patients showed picture of aspirin resistance throughout the postoperative course even though a normal reaction towards aspirin before surgery. The resistance developed gradually after surgery (Figure 5), breaching the 30%-threshold by 5th postoperative date. As shown in Table (2) *the use of cardiopulmonary bypass, pump time and type of procedure (Isolated CABG or combined with valve) showed no influence on the resistance rate.*

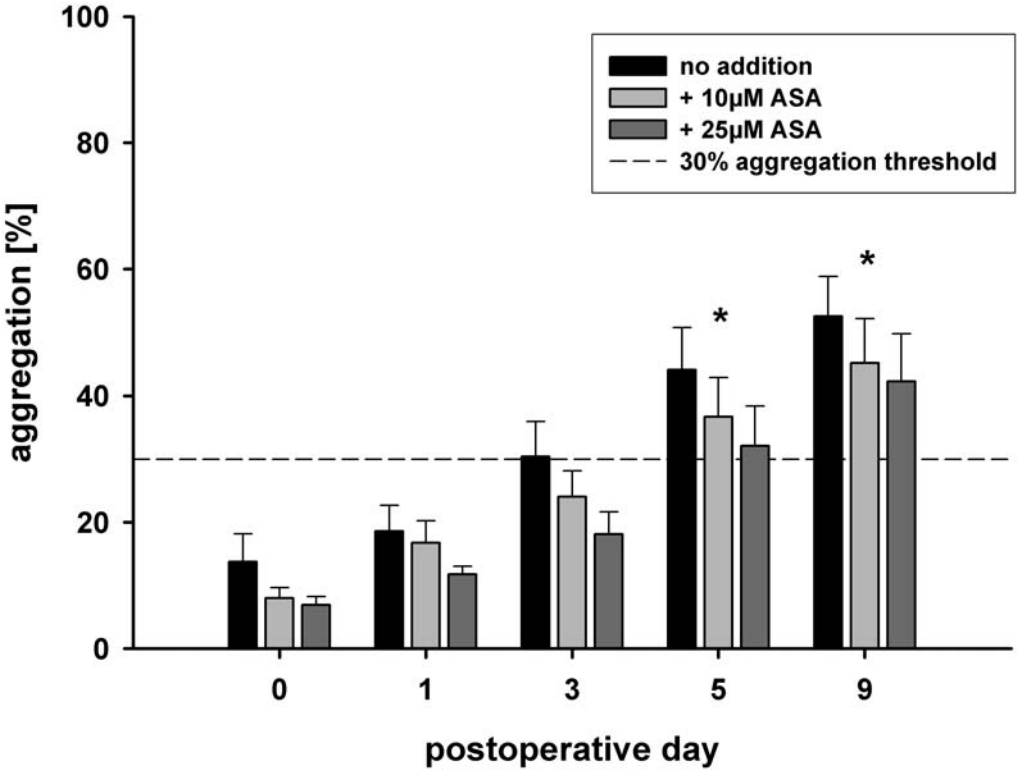

Figure 5. Arachidonic acid induced aggregation in postoperatively resistant patients (n=51)
*** p<0.05 vs. before surgery (day 0)**

One year follow up showed 5 deaths. Major cerebrovascular accident was encountered in 2 of them proved by CT-scan (first patient developed the event in the 5th post operative date and second one on the 9th day). One patient developed acute renal impairment on the 3rd day post operative that progressed to be end stage and causing multiorgan failure. The fourth patient suffered from severe postoperative wound infection that caused mediastinitis and septicemia. The 5th patient suffered from a cardiogenic shock which was expected (high risk patient) after a difficult recovery from the CPB. Perioperative aspirin resistance was found in all the death cases while patients with normal reaction to Aspirin showed no mortality. Two other patients suffered from transient ischemic attacks in resistant group and recovered completely. The aspirin resistance disappeared completely after one year in the group that developed it in the perioperative period.

Discussion

Aspirin resistance is roughly defined as inability to prevent thrombosis in all patients[1]. In general, patients that experienced ischemic attack despite the fact that they were on aspirin treatment might be considered as resistant to Aspirin. Failure to suppress platelet aggregation through inhibition of platelets cyclooxygenase-(COX-) 1 together with prevention of thromboxane A2 formation is the pharmacological basis responsible for the resistance. Considerably aspirin resistance should be distinguished from the treatment failure[2]. In general 3 types of pharmacological resistance were described[11]; the pharmacokinetic resistance (type 1) where aspirin works after addition in vitro but not in vivo, pharmacodynamic resistance (type 2) where in spite of adequate concentrations in the plasma still it is unable to suppress the activity of COX-1, the pseudoresistance form (type 3) where platelets are activated (regardless of the aspirin effectiveness) through a mechanism independent of thromboxan. Resistance to Aspirin has been described in the postoperative period following CABG surgery and suggested to be a temporary event[12, 13]. The basis of this resistance is attributed to the pharmacodynamic failure (type 2)[9]. As our patients showed a restricted response to the in vivo added ASA (even with addition of high doses) we would so much support the contemplation that resistance in CABG surgery belong to type 2.

Although the exact mechanism of aspirin resistance remains unclear[14], several theories have been suggested. Increased in the platelets activity together with the major increase in the COX-2 expression might be a possible cause[15, 16]. Insufficient inhibition of platelet COX-1 might be another mechanism suggested by Zimmermann et al.[17] Some authors suggested polymorphism of the COX-1 gene itself[18] or of platelet membrane proteins (19). One study reported mechanism related to ADP pathway but not for COX-1 and COX-2[20]. Platelets of aspirin resistant patients showed to be more sensitive and activated straightforwardly through ADP pathway[21, 22] which very much support the above hypothesis. Our findings that aspirin resistance is transient and absent after 12 months support the idea that the cause is most probably related to surgical factors which is consistent with what have been previously described[12, 13].

Aspirin resistance was present in 27 of patients prior to surgery (27%). In comparison to other reports the total rate seems to be reasonable[5]. It was clear that ASA treatment before surgery has positive significant impact since there was a dramatic increase in the resistance rate (83%) in patients who stopped Aspirin several days ahead of surgery where this might be attributed to paradoxical rebound platelet activation after stopping COX inhibiting drugs. The paradoxical rebound phenomena have been described for both Aspirin and other COX-inhibitors[23, 24].

Up to 50% of patients in our study developed aspirin resistance after surgery which resemble others results[10, 13] but in contrast to previous findings[9] off-pump approaches or extensive pump-times had no statistical impact on resistance rates in our series. As aspirin resistance is found in considerable number of our patients after off pump surgery, some other groups also support the idea that the resistance is not restricted for the on pump procedures[13, 25]. Patients undergoing off pump CABG and having preoperative resistance are not liable for higher myocardial injury[26].

Aspirin resistance gained a lot of interest in the recent years because of the growing concerns about the mortality and ischemic infarcts that may cause. It is back to 1993 where an important report alerts the risks of in-vitro resistance to aspirin manifested by increase in myocardial infarction, recurrent stroke and

death[27]. In patients undergoing percutaneous coronary interventions the incidence of myocardial infarction is higher in the resistant group[28]. Similar results with higher re-occlusion rates have been described in resistant patients after balloon angioplasty as a treatment for intermittent claudication[29]. Lately some suggest a higher risk of death, stroke or myocardial infarction even in patients that show weak reaction to aspirin[30].

Since almost up to 75% of our patients developed resistance pre (24%) or post operative (51%) and only 25% showed a normal reaction, it is clear that resistance in patients undergoing CABG is a very serious issue. During the one year follow up there was five deaths in resistant group while none in patients that showed normal reaction to Aspirin which might imply important impact on the clinical outcome. The association between aspirin resistance and early vein graft failure after CABG is significantly correlated[26] and matches with our results. The addition of Clopidogrel postoperatively as a treatment option might improve the mid term outcome after CABG[31] and this might be related to the increased –ADP-sensitivity of resistant patients[20].

A newly published study suggested a transferable plasma factor which intervened the plasma hyporesponsivness to ASA[32] where previously there was no evidence for inheritance or acquired aspirin resistance[14].

The use of intravenous ASA for reduction of laboratory aspirin resistance after CABG procedure seems to be promising and effective[33, 34].

The low number of patients is considered as one of the study limitations, for that reason, future studies need to be conducted with larger patient cohorts and on randomized basis. The addition of further antiplatelet therapy e. g. Clopidogrel may be needed in selected patients following clarification of aspirin resistance impact on clinical outcome. The benefit of taking aspirin at the time of surgery on the survival rate is already confirmed[8, 35, 36]. After cessation of ASA therapy, the transient aspirin resistance could be attributed to platelet rebound activity as a possible mechanism of action. In order to test the patients for aspirin-resistance after CABG, we would suggest using the turbidometric method described here on the 5th postoperative date.

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مقاومة الأسبرين في المرضى الذين يخضعون لعملية تطعيم الشرايين التاجية

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الملخص

الهدف: مقاومة الأسبرين في المرضى الذين يخضعون لعملية تطعيم الشرايين التاجية. الأسبرين، هو الدواء الشائع جداً الذي يستخدم بعد تطعيم الشرايين التاجية، ومعروف للحد من وفيات ومعدل حدوث مضاعفات نقص التروية بعد تطعيم الشريانات التاجية. مقاومة الأسبرين هو موضوع معروف جيداً، ولها تأثير كبير على النتائج السريرية. وهدفت الدراسة إلى التحقيق في ظاهرة مقاومة الأسبرين في مرضانا بعد خضوعهم لجراحة تغيير الشرايين التاجية. شملت الدراسة 100 مريض خضعوا لتطعيم الشرايين التاجية للتحقيق في حساسيتهم للأسبرين باستخدام الصفائح الدموية لدراسة قياس التكدس. وتمت متابعة المرضى بعد سنة واحدة لإظهار نتائجها السريرية.

أظهر 25 مريضاً (25%) رد فعل طبيعي على مقاومة الأسبرين (حساسية للعلاج)، وكان 24 مريضاً (24%) مقاوم للأسبرين قبل الجراحة، بينما أظهرت أن (51%) اكتسبوا هذه المقاومة بعد العمل الجراحي. لم يظهر استخدام جهاز القلب والرئة الصناعي ووقت المضخة ونوع الإجراء أي تأثير على معدل المقاومة. بعد سنة واحدة من المتابعة كانت هناك خمس حالات وفاة في مجموع المرضى الذين أظهروا المقاومة قبل الجراحة، في حين أن المقاومة اختفت تماماً بعد سنة واحدة في المجموعة المتعلقة بالجراحة.

مقاومة الأسبرين تحدث في جزء كبير من المرضى الذين يخضعون لجراحة القلب المفتوح لتطعيم الشرايين التاجية. لا يبدو أن المقاومة تستمر بشكل دائم، وإنما لفترة وجيزة. ويمكن التنبؤ بنتيجة أسوأ للمرضى الذين يعانون مقاومة الأسبرين من خلال زيادة الوفيات في هذه المجموعة.

الكلمات الدالة: الأسبرين، عملية تطعيم الشرايين التاجية، مقاومة.

