

Therapy with acetylsalicylic acid does not interfere with oral surgery

Research Article

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Abstract: The acetylsalicylic acid (ASA) treatment is widespread therapeutic strategy in cardiology clinics. On the other hand, patients with heart diseases represent a significant group of cases in dental clinics. Accordingly, we studied the local hemostatic thrombus formation after dental tooth extractions (n=47) and other oral surgery treatment (n=13) in 60 patients with heart disease being on ASA therapy without drug discontinuation. In the control group free of ASA therapy it was: (n=24) and (n=6), respectively. In all studied patients, the aggregative activity of blood platelets by PFA-100 analyzer was assessed. It was found that 61.7% patients treated with ASA presented inhibition of platelets aggregation. Unexpectedly, in 35% of such patients, platelet aggregation function remained unchanged. In the control group, normal platelet aggregation was found in all subjects. It has been shown that ASA therapy has neutral effects on both thrombus formation and pain complications in patients with heart disease underwent tooth extraction and other oral surgery. Thus discontinuation of ASA therapy before surgery seems to be weakly validated.

Keywords: Platelets • Acetylsalicylic acid • Oral surgery • Dental tooth extraction

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1. Introduction

Hemostasis is a physiological condition responsible for dynamic interaction between coagulation and fibrinolysis, preventing uncontrolled hemorrhage events. The activation of coagulation is characterized by a sequential activation of a series of serine proteases with final thrombin generation and conversion of fibrinogen into an insoluble thrombus [1]. During the formation of a thrombus the activated platelets play a central role. However, these same pathways regulating hemostasis lead to pathological thrombosis and vessel occlusion. Therefore, advances in understanding the mechanisms

regulating thrombosis have led to development new classes of antithrombotic drugs. However, cyclooxygenase inhibitors, most notably acetylsalicylic acid (ASA), still play a significant role [2,3].

Acetylsalicylic acid is one of the most commonly used medications belonging to a group of non-steroidal anti-inflammatory drugs [3]. ASA permanently inactivates cyclooxygenase (COX-1), inhibiting the formation of platelet-specific eicosanoid thromboxane A₂ from the liberated arachidonic acid [4,5]. Consequently, there is a permanent and complete blockage of platelet aggregation activity. Inactivation of COX-1 is irreversible and detectable after 1 h administration of a single dose of

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100 mg. Its effect lasts for at least 7 days but after about 5-6 days 50% of the platelets may exhibit normal aggregation activity [6,7].

The ASA-based therapy is one of the major therapeutic strategies in cardiology departments. On the other hand, such cohort of patients represents a significant group of subjects in dental clinics, as well. In patients with heart disease the ASA dose of 75-160 mg is most often used. It should be emphasized that the response of platelets to ASA is an individual feature associated with impaired sensitivity or "resistance" of platelets to ASA. This phenomenon is more common in patients with coronary artery disease than healthy subjects and may be observed in up to 45% of cases [8-10]. Interestingly, it was found that the "resistance" is nearly two times greater at a dose below 100 mg compared to a dose of 150 mg [11,12]. The platelet function analyzer PFA-100 (Dade Behring Marburg GmbH) gives possibility to monitor the effectiveness of ASA therapy [13,14].

In current strategies of preventing embolic events in surgery, maintenance of ASA therapy is routinely recommended. Unfortunately, in practice it is not such obvious. Controversies stem from the fact of a potential risk of bleedings in patients receiving long-term ASA. To address this issue, we studied the local hemostatic thrombus formation and possible local bleeding after dental extractions and other oral surgery of patients with heart disease being on ASA therapy.

2. Materials and methods

In the current study 60 patients (37 M, and 23 F; aged between 33 - 86 years; mean age 62.9 years) from the Silesia region were finally enrolled. Patients were on chronic (> 6 months) antiplatelet therapy with ASA for prevention of ischemic heart disease. The control group for the platelet function assessment by PFA-100 analyzer consisted of 30 healthy individuals (18M, 12 F, aged 27 - 75 years; mean age 53.9 years). The inclusion criteria were as follows: (1) the presence of heart disease, (2) the chronic (> 6 months) ASA therapy, and indication for surgery in the oral cavity. The exclusion criteria were as follows: (1) the disruption of ASA therapy before and after oral surgery, (2) withdraw agreement at any study stage, and (3) the usage of other than ASA, antiplatelet and anticoagulants drugs. In the study group tooth extractions (n=47) and other oral surgery treatment (n=13) was performed. In the control group, it was (n=24) and (n=6), respectively (Table 1).

The blood samples (10 ml venous blood per patient) were immediately chilled to 4°C, centrifuged, and analyzed immediately or frozen at -70°C until analysis. In

Table 1. Characteristics of the control and study group.

Quantity of patients	Study group n=60	Control group n=30
Age(years)	33 – 86	27 – 75
Mean Age (years)	62.9	53.9
Sex F/M	23/37	12/18
Tooth extractions	31	20
Surgical extractions of the third molars	16	4
Evacuations of the cyst	4	2
Excisions of the mucosa hypertrophy	2	2
Operations of the maxillary sinus	3	1
Surgical treatment of the oral cavity trauma	4	1
Surgical procedures with suturations of the wounds	43	14

addition to the routine biochemical examinations, 4 ml of venous blood were collected in tubes of buffered sodium citrate in order to assess platelet function by PFA-100 analyzer (Dade Behring Marburg GmbH). The platelet function is determined in the whole blood samples by determining of a closure time (CT) after collagen/epinephrine (Normal CT: 85-165 sec) and collagen/ADP (Normal CT: 71-118sec) platelet stimulation. The collagen/ADP test very likely determines the platelet dysfunction due to ASA [15-17]. Method of testing platelet function analyzer PFA - 100 is shown schematically in Figure 1.

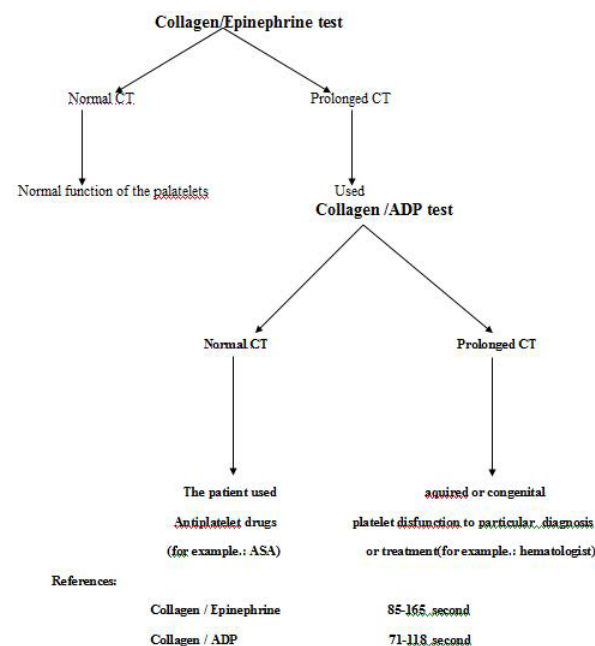


Figure 1. The interpretation of the CT test in PFA-100.

After dental extractions and other surgical procedures, the operating field was protected by a sterile gauze for 30 minutes or supplied with single stitches us-

ing sterile resorbable monofilament thread a 3-0, 4-0. All procedures were performed under local anesthesia, using 2% Lignocain, only. All patients received amoxicillin or clindamycin (first dose of antibiotic was administered 2 hours before surgery) for 7 days, due to their underlying disease.

In the control group antibiotic cover was inserted prior to the removal of impacted teeth ($n=4$), cystectomy ($n=2$) and the revision of the maxillary sinus ($n=1$). Local bleeding from the sockets and surgical wounds was evaluated based on the three-point scale: 0° - no bleeding; I° - seepage or bleeding by applying drops of the continuing pressure dressing and / or individual sutures, which require additional supplies such as topical haemostatic agent and / or use of haemostatic sutures type "z"; II° - bleeding requiring a larger volume of the above, local procurement or intravenous pharmacotherapy (etamsylate). Evaluation of episodes of bleeding was carried out after 30 minutes, 1, 3, 7 and 10 days after surgery together with "percolation" test, i.e. the number of swabs needed to stop bleeding. For postoperative discomfort, all patients were evaluated after 30 minutes, 1, 3, 7 and 10 days after surgery, using 100-millimeter Visual Analog Scale (VAS) (0 mm - no pain to 100 mm - the strongest occurring disorders). Also, the semi quantitative scoring scale was used for assessing discomfort feeling (0 - no symptoms, 1 - moderate discomfort, 2 - discomfort of moderate intensity, 3 - severe discomfort). The decrease in the intensity of postoperative discomfort was estimated in the three-point scale (0 - complete spontaneous remission of symptoms, 1 - symptoms subside after the application of short acting oral non-steroidal anti-inflammatory drugs (NSAIDs), 2 - symptoms subside after short-NSAIDs or after application of narcotic analgesics i.v.). Equipment was removed from the surgical wound on the seventh day after surgery. In order to reduce postoperative discomfort, meloxicam (NSAID) was used at a dose of 15 mg daily for 7 days. To reduce discomfort, meloxicam 15 mg/day for 7 days was prescribed. The protocol was approved by the institutional Ethics Committee.

For statistical analysis Statistica 6.0 PL was used. After determining the distribution, the Kolmogorov-Smirnov test was applied for data of normal distribution and the Mann-Whitney test for data other than the normal distribution. For correlation analysis Pearson linear correlation test was applied. In comparison to the size of the groups examined the chi-squared test was used. The results were presented as a mean, standard deviation, absolute number and percentages. A level of $p<0.05$ was considered statistically significant.

3. Results

The results of platelet aggregation function by PFA – 100 are shown in Figure 2. In 37 patients (22 M, 15 F; 61.7%) the CT was prolonged when trying with Collagen / Epinephrine but it was corrected when using Collagen / ADP, confirming the effectiveness of blocking platelet function by ASA. Interestingly, in 21 cases (13 M, 8 F; 35%) CT was normal in Collagen / Epinephrine, which indicated the presence of platelet resistance to ASA drugs. In 2 patients (2 M; 3.3%) pre-laboratory error disabled CT reading. The entire control group presented normal CT when trying Collagen / Epinephrine, which confirmed normal function of platelets.

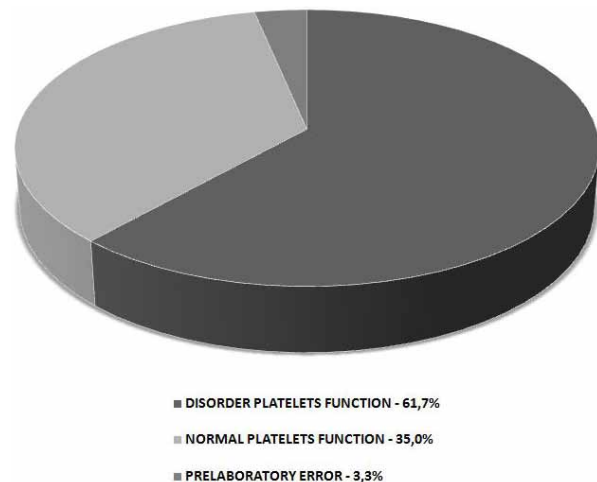


Figure 2. Graphical results of the CT test in the study group.

After 30 minutes of surgery there was no local bleeding, neither in the patients with impaired platelet aggregation, nor in ones with preserved ability of platelets to aggregate. The average of 3 ± 1 sterile swabs were used in the "percolation test" for the entire group to obtain blood clot in the time of 30 minutes (NS). Similarly, no local bleeding was observed within 24 hours after surgery. At this time, all patients presented normal wound healing. Likewise, clinical evaluation at 3-, 7-, and 10-day after surgery showed no hemostatic complications and postoperative discomfort remained at the same level as on the first day. The proper tooth socket healing was observed in all patients.

As in the study group, in the control group an average of 3 sterile swabs ± 1 were used in the "percolation test" to obtain a blood clot after 30 minutes of surgery. In addition, no haemostatic complications were observed at this time of study. Similarly, no bleeding was recorded at the time of remaining follow-ups in the control group.

After 24 hours of surgery, 15 subjects from the study group had post-operative discomfort presented as a moderate intensity pain. The intensity of discomfort referred to the VAS ranged from 20 to 30 millimeters, while on the scale of discomfort feeling it was moderate. Among patients who had post-operative discomfort, only 4 of them were reported as having moderate severity of it. Such discomfort resolved spontaneously within 10 days after surgery.

4. Discussion

The current study confirmed previous observations about the lack of association between the continuation of antiplatelet therapy with ASA preparations and an increase incidence of local bleeding after oral surgery. It has been shown that despite the impaired activity of platelet aggregation to clot formation, the proper wound healing occurred. Unexpectedly, the use of PFA-100 analyzer could detect platelet resistance to ASA in part of studied patients suffering from cardiovascular diseases. It may have a significant impact on clinical outcome of patients treated long-time with ASA.

Similarly to our study, Bielecka - Cieslik A., *et al.*, reported no significant relationship between the use of anticoagulants (including ASA preparations) and the occurrence of local bleeding in 40 patients [18]. Likewise, Hemelik M., *et al.*, observed a similar rate of complications after teeth extractions in 65 patients taking ASA at a dose of 100 mg daily as a secondary prevention of coronary heart disease. The percentage of bleedings in the study group was 1.54% as compared with 1.58% in the control group [19]. Two other studies have shown the same results in different clinical settings suggested no necessity to withdraw the antiaggregation therapy before oral surgery [20,21]. However, the clinical observations in all mentioned studies were not supported by the assessment of platelet function in laboratory studies. It should be noted that there are a several case study reports describing haemostatic complications after oral surgery in patients taking ASA. Accordingly, Thomason JM., *et al.*, [22] reported massive bleeding after surgical gingivectomy in the anterior maxilla in 30-year-old man undertaken kidney transplantation, who was treated chronically with ASA at a dose of 150 mg daily. After 40 minutes of surgery, bleeding occurred and was successfully treated with transfusion of 6 units of platelets. Laboratory test showed impaired activity of platelet aggregation in this case. Similarly, Lemkin SR

et al., presented a case report of a patient who required transfusion of platelets to achieve correct hemostasis [23]. Other authors have noted similar cases of hemostatic complications after oral surgery [24]. However, it should be emphasized that these case reports did not apply to patients with ischemic heart disease using low-dose ASA i.e. <100 mg per day.

Until recently, in the general surgery there are different opinions on termination or continuation of ASA therapy. Accordingly, Mak S. and Amoroso P. recommended discontinuation of antiplatelet therapy on urological surgical treatment because of the possibility of bleeding after procedures such as prostatectomy [25]. Richardson *et al.*, also argued in favour of the discontinuation of antiplatelet therapy for 7 days before scheduled surgical procedures [26]. In the cardiac surgery, discontinuation of ASA therapy seven days prior to the planned treatment was considered as the standard, due to the possibility of complications such as bleeding and the need for re-operation or blood transfusion [27]. However, Bybee KA., *et al.*, conducted a prospective study of 1636 patients who underwent isolated CABG (coronary artery bypass grafting). In the study, 1316 patients received ASA within 5 days prior to cardiac surgery, while 320 patients discontinued ASA therapy. All patients received 6 hours after surgery an oral dose of 81 mg ASA and 325 mg 24 hours after surgery. Tranexamic acid was routinely used intra-operatively. In the whole study group 36 deaths and 48 cases of cerebral complications were recorded. It was shown that the use of preoperative ASA significantly reduced the risk of postoperative mortality and stroke compared with the group in which such procedures were not applied (1.7% to 4.4%) [28]. Other studies by Samama CM., *et al.*, [29] strongly supports the view of maintaining antiplatelet therapy before surgery with reference to the guidelines of the French Society of Anesthesiology and Intensive Care.

Concluding, the most previous reports which recommended maintenance of ASA therapy before and after oral surgery based on clinical observations without verification of platelet aggregation activity [18-21,30]. The using of PFA-100 analyzer enabled us to directly confirm that despite impaired platelet aggregation by ASA no hemostatic complications after oral surgery in such patients were observed. Overall, the available data including current results are compatible with the concept that continuations of ASA therapy neither increase the risk of bleeding, nor delay complications after oral surgery in patients on ASA therapy.

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