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Is PFA-100® ADP/Epinephrine Platelet Aggregometry a Helpful Tool in Neurosurgical Patients on Acetyl Salicylic Acid Medication?

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Abstract

Objectives: Due to an aging patient population, neurosurgeons are increasingly confronted with patients taking Acetylsalicylic Acid (ASA) as an antiplatelet agent. Since a normal platelet function is frequently deemed necessary for neurosurgical interventions, the usefulness of the PFA-100® test to evaluate the platelet function is assessed.

Methods: We retrospectively evaluated data on all neurosurgical patients subjected to a PFA-100® Platelet Aggregometry (PA) test between 6/12 and 2/17 and noted the reasons the test was done, the time required for platelet function to normalize, and how well the test results correlated with intra- and postoperative findings.

Results: PA had been performed on 171 patients, the reason being ASA treatment in 154 and coagulation analysis in 17. The PAs of the operated patients admitted for emergency treatment normalized between 0-19 days after ASA withdrawal (53%: 0-3, 34%: 4-6, 6%: 7, 7%: >7 days). With a mean of 3.7 days, the average time was found to be considerably shorter than the expected 7 days. 144 ASA patients underwent surgery. None of the 124 patients with normal and 3/20 with abnormal PAs had to be re-operated on.

Discussion: Since normal PA test results correlated well with uncomplicated surgery, the study suggests that the test might be a reliable tool to time an operation in neurosurgical ASA patients. As 87% of the patients regained a normal platelet function in less than 7 days, the interval between last ASA administration and a neurosurgical procedure can often be reduced.

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Introduction

Due to the ageing of the population and, coupled with this, its accompanying age-related comorbidities, neurosurgeons are increasingly being confronted with patients on Antiplatelet Agents (AA). Although various new oral antiplatelet medications have become available, Acetyl Salicylic Acid (ASA) is still the most frequently prescribed AA monotherapy. In general, neurosurgeons and neuro-anesthesiologists are well aware that ASA medication may be accompanied by an increased risk of perioperative bleeding complications in spinal as well as in intracranial surgery. As early as 1979 Merrimen et al. [1] called attention to the fact that not only high analgesic, but also low ASA doses should be noted with concern. In a 1997 survey of the views and practices of neuro-anesthesiologists in the UK, James et al. [2] found that 44% of the responders considered ASA to increase the risk of hemorrhagic complications in patients undergoing intracranial procedures. 12.9% reported having personally experienced such cases, but only 27.6% had a personal and 5.2% an official departmental policy to discontinue ASA treatment preoperatively. Ten years later, Korinth et al. [3] sent a questionnaire to 210 German neurosurgical facilities in order to assess current treatment guidelines. They received 142 valid answers, 80.3% of which stated that their departmental policy was to discontinue ASA before surgery. In 2020, however, treatment strategies still vary significantly among different German neurosurgical centers as stated by Skardelly et al. [4]. In a recent survey evaluating the management of perioperative bridging of anticoagulation and antiplatelet therapy in neurosurgical interventions, 60.7% of the participating centers had no defined policy. In the subgroup of patients at high risk for thromboembolism, ASA was discontinued in 22%, bridged in 35%, and continued in 35% of the responding centers.

In addition to these highly variable expert opinions, decision making is rendered even more

difficult by the fact that statistically valid data on the actual risk of clinically relevant bleeding complications in neurosurgical patients on ASA is sparse for both spinal as well as intracranial surgery. A recent prospective trial by Akhavan-Sigari et al. [5] on the limited number of 100 patients who continued taking ASA and/or clopidogrel while undergoing various procedures for degenerative spinal disorders found a 6% risk of subcutaneous hematomas but no postoperative bleeding with neurological deterioration or a need for evacuation. A further recent prospective study was conducted by Cuellar et al. [6] on patients with cardiac stents undergoing spinal surgery. They found no difference in estimated blood loss, the amount of blood products transfused, and the overall intra- and postoperative complication rate comparing 100 patients who continued daily ASA with 100 patients who discontinued the drug preoperatively. A closer look at the data, however, reveals, that the ASA patients had a shorter average hospital stay (4.1 ± 2.7 *vs.* 6.2 ± 5.8 days), duration of surgery (210 ± 136 *vs.* 266 ± 143 min) and a lower estimated blood loss (642 ± 905 *vs.* 697 ± 1187 ml). This gives rise to the assumption that patients of the ASA and non-ASA group were not well matched. In conjunction with the exceptionally high standard deviations listed above this study is considered to be of limited significance. Kang et al. [7] reported on the contradictory findings of a significantly increased blood drainage after spinal fusion surgery even in patients stopping ASA at least 7 days prior to surgery as compared to non-ASA patients while the intraoperative blood loss was comparable in both groups.

A retrospective study by Rahman et al. [8] analyzing the effects of perioperative ASA on clinical outcomes in patients undergoing craniotomy for brain tumors found no statistical difference with regard to clinical outcomes among the three ASA-treatment groups: Those not on ASA (368 patients), those who discontinued ASA preoperatively (55 patients), and those who continued taking ASA (28 patients). The study evaluated bleeding complications, the need for reoperation, and thrombotic complications. However, there were too few patients in the ASA groups to draw a generalized conclusion. On the other hand, Chen et al. [9] reported that patients taking ASA had an increased risk of secondary hemorrhage after surgery for hypertensive cerebral hemorrhage. With a 19.4% risk in the ASA group as compared to a 10.2% risk in the non-ASA group, the difference was found to be statistically significant ($p<0.05$). Comparing these data to those of Lillemäe et al. [10] with an 0.6% overall risk of postoperative hematoma requiring reoperation after craniotomy, both rates seem to be exceptionally high. A closer look at Chen's data [9] reveals that there is neither information about the clinical relevance of the secondary bleedings nor about the necessity of reoperation.

Summarizing these unsatisfactory data, at this point in time, one could assume that it might be more important to discontinue ASA for intracranial surgery as compared to spinal surgery. Since some of the data are contradictory, they need to be confirmed by further studies.

Thus, until reliable data or even guidelines are available, neurosurgeons need to decide on an individual basis whether to stop ASA prior to surgery. If discontinuation of the drug is deemed necessary, the next step is to determine the optimal time to operate. In most cases, this will be the earliest possible date for various reasons. For instance, cardiologists will recommend keeping the ASA-free interval as short as possible in patients who would have an increased risk of thromboembolic complications. In addition, in patients admitted with neurological deficits, these are more likely to be reversible the earlier the operation is performed. And finally, in times of DRG-related reimbursement, it is in the financial interest of the hospitals to keep the preoperative waiting time of in-patients as short as possible.

Unfortunately, validated information on the optimal interval from last ASA intake to the date of neurosurgical operations is sparse as well. In cranial surgery, James et al. [2] reported on a suggested mean time of 11.3 days, ranging from 1 to 42 days. Korinth et al. [3] found a mean interval of 6.9 days, ranging from 0 to 21 days, but once again, these data are merely based on expert suggestions or departmental policies.

Therefore, in order to schedule operations in neurosurgical ASA patients individually, a reliable routine laboratory test to assess the current platelet function would be helpful. One candidate procedure, PFA-100® platelet aggregometry is the most frequently used primary hemostasis-screening instrument [11]. It has been considered helpful in monitoring the efficiency of ASA in non-neurosurgical settings. Homoncik et al. [12] found the PFA-100® system to be suitable for demonstrating an ASA-induced platelet effect in a longitudinal study and deemed it adequate to monitor patients' compliance. Reny et al. [13] demonstrated that a short PFA-100® closure time (CEPI) indicating a normal platelet function is associated with an increased recurrence of ischemic events in ASA-treated cardiovascular patients. Coma-Canella et al. [14] found that the procedure could be used to identify cardiology patients with ASA resistance amounting to 32% of their cases. Analyzing platelet function in patients qualified for trauma and orthopedic surgery procedures, Kurak et al. [15] however, criticized, that patients with normal PFA-100® test results despite ASA therapy amounting to 37% of all ASA patients exhibited significantly more intense bleeding after dynamic hip screw surgery. They claimed that normal PFA-100® test results could not be explained by ASA resistance but were only a laboratory phenomenon.

The purpose of this investigation is therefore to evaluate the usefulness of ADP/epinephrine platelet aggregometry using the PFA-100® system in neurosurgical ASA patients with a particular focus on its potential benefit in optimally timing neurosurgical interventions.

Material and Methods

We retrospectively analyzed the data on all neurosurgical patients undergoing CEPI/CAPD platelet aggregometry using the PFA-100® test between June 2012 and February 2017 at the Municipal Hospital Solingen.

The PFA-100® system is a commercially available automated, rapid, low-cost test based on the property of platelets to adhere upon shear stress conditions and aggregate in consequence of agonist presence in the system [16]. A citrated whole blood sample is aspirated at a high shear stress rate into a cartridge containing a biologically active membrane. This membrane is coated with either Collagen and Epinephrine (CEPI) or Collagen and ADP (CADP), and it has a defined microscopic aperture, thus mimicking a small lesion in capillary endothelium. Formation of a platelet plug is induced, which leads to occlusion of the aperture. The Closure Time (CT) is measured. As a first step, the test is performed with epinephrine. If this test is normal, clinically relevant platelet dysfunction can be excluded, the test having a high negative predictive value [16]. If the CT is prolonged, a second test with ADP is performed. If this test is normal, the two tests combined indicate that the platelet dysfunction is ASA-induced. If both tests show a prolonged CT, the platelet defect

is not related to aspirin. The reference range for the CEPI test is from 85 up to 165 sec, for the CAPD test from 71 up to 118 sec. The test is reliable only if the hematocrit is >35 and the platelet count >150/ nanoliter.

We assessed the reasons why the test was performed, the time needed for the test results to normalize after the last dose of ASA, and the correlation between normal test results and intra- and postoperative bleeding complications.

When requested in ASA patients, the test was performed on the day of admission. If pathological, it was repeated until the result returned to normal. The additional tests were performed one or several days later depending on the exact closure times of the first test but not daily. Therefore, the number of tests run per patient varied between 1 and 6.

Results and Discussion

Between June 2012 and February 2017, 171 neurosurgical patients underwent the PFA-100® test, the number rising from year to year as confidence in the test increased. Figure 1 shows the distribution of the underlying diagnoses, spinal disorders representing the largest group followed by brain tumors. The test was not reliable in 12.3% of the patients (7 cases with low platelet count, 10 with a hematocrit ≤ 35 and another 4 with both).

Indication for the test

In 154 patients, the test was performed due to ASA therapy. Among those, 146 were taking ASA as an AA and 8 for pain relief. In the remaining 17 cases, the test was performed as part of a coagulation analysis.

ASA patients were divided into the two subgroups of scheduled versus emergency patients. Scheduled patients discontinued ASA 7 days prior to admission. Emergency patients had usually taken the drug till the day of admission. In these patients, the time interval from last drug administration to a normal test result was evaluated, based on documentation of the last day of ASA intake in the case files.

ASA patients: Emergency admissions

Of the 114 emergency admissions on ASA, 106 underwent surgery, and of these, 20 prior to their tests becoming normal owing to medical urgency. In the other 86, the operation could be delayed until their PA had normalized. Figure 2a and 2b illustrate the time required for these PAs to return to normal: 87% (75/86) of the patients needed fewer than the expected 7 days and 53% (46/86), between only 0 to 3 days. In 7% however, the results were still abnormal after 7 days and these patients needed up to 19 days for their PAs to normalize. The median was 4, the mean value 3.7 days.

Eight of the emergency admissions on ASA were treated conservatively: One who had had an intracranial hemorrhage under efficient platelet inhibition, one patient with a herniated lumbar disc for whom the cardiologists strongly advised that combined antiplatelet agent therapy with ASA and clopidogrel be continued, and six patients whose symptoms improved significantly and who were no longer considered candidates for surgery.

ASA patients: Scheduled admissions

Among the 40 scheduled ASA cases, PA was normal at admission in 36 whereas it returned to normal only after 9 and 10 days in 2. In a further 2 cases, both the CEPI and the CAPD test were abnormal indicating that patients had other, ASA-independent coagulation

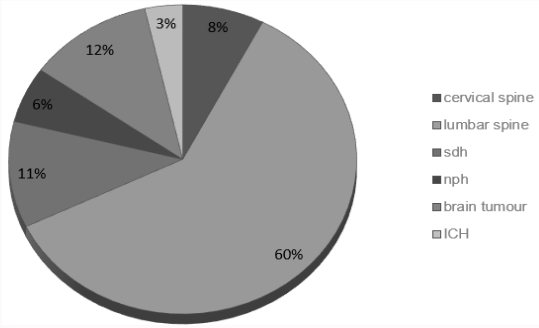

Figure 1: Patient's distribution to diagnoses.

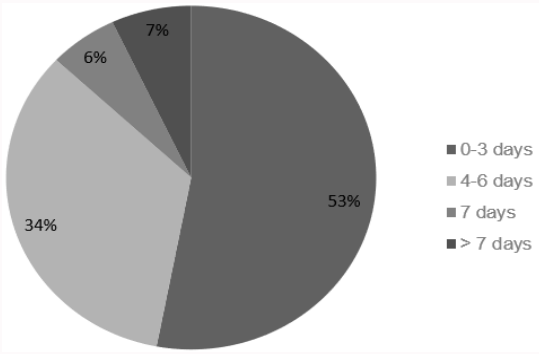

Figure 2a: Duration from last antiplatelet agent intake to test normalization in emergency patients.

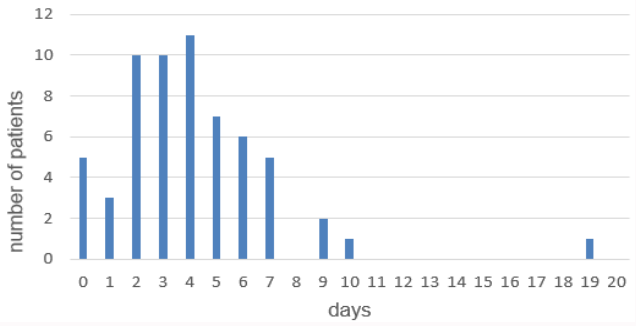

Figure 2b: Duration from last ASA intake to normal PA test in operated emergency patients.

disorders, and these patients were treated conservatively.

Coagulation analysis

Out of the 17 patients, 10 had PA tests performed preoperatively due to a clinical history of an increased bleeding propensity. Out of these, only two patients were not operated on, one of them a glioblastoma patient with persistent thrombocytopenia. In two cases, the test was performed intraoperatively and in 5 cases postoperatively due to profuse bleeding during surgery. In the first intraoperative cases, the result of the CEPI test was >300 while the CADP test was normal. The operation was discontinued after one level instead of the planned two, and various hemostatic agents including systemic application of tranexamic acid were necessary to achieve hemostasis. The patient denied taking ASA but was treated with ibuprofen preoperatively. The test results returned to normal six days postoperatively and proved to be normal at a later readmission, thus indicating that the disorder might have been related to the antiplatelet effect of ibuprofen. In

the second intraoperative case, profuse bleeding not only from the epidural veins but also from the bone was observed in a patient operated on an intraforaminal lumbar disc herniation. The result of the CEPI test was 193 while the CAPD test was normal. The patient had as well been on ibuprofen preoperatively and hemostasis could be achieved with the help of an absorbable hemostatic gelatin sponge.

Correlation between test results and intraoperative findings

None of the 124 ASA patients operated with normal PA test results had to be re-operated on. Surgery reports of the 38 scheduled patients did not mention any difficulties to achieve hemostasis. Among the 86 emergency patients, three were reported to have increased but surgically manageable intraoperative bleeding. A closer look at these 3 patients revealed, that 2 were operated on for spinal stenosis. One of these required 19 days from the last dose of ASA for the test result to normalize. This observation suggests that hemostasis may have been influenced by additional factors. During surgery, no special hemostatic agents were necessary in the 2 spinal stenosis cases, however. The third patient underwent surgery for a cervical intraspinal joint cyst *via* a dorsal approach in the prone position, in which bleeding from the epidural venous plexus is a common finding. Intraoperative hemostasis could be achieved using a fibrin sealant patch. None of these three patients had postoperative complications.

Of the 20 patients taking ASA and operated on in spite of pathological PAs, 2 with an acute and 1 with a chronic subdural hematoma needed to be re-operated on due to secondary bleeding. One of the patients with an acute subdural hematoma had non-Hodgkin's lymphoma and the PA was considered unreliable due to a thrombocytopenia of 74/nl. The patient eventually succumbed to an intraparenchymal intracranial hematoma despite being re-operated on and receiving repeated transfusions of pooled thrombocyte concentrates.

The idea that, if discontinued, ASA should be stopped about 7 days preoperatively is based on the average platelet life span, which ranges between 7 and 10 days. Given that ASA has a short half-life in plasma and that it irreversibly inhibits thrombocyte cyclooxygenase, the antiplatelet effect should end when all thrombocytes have been replaced. A recent trial by Nayak et al. [17] using a murine model and human platelets *in vitro* indicates that ASA might also limit the platelet life span by proteasomal inhibition. It was shown that ASA-treated human platelets were phagocytosed more efficiently by macrophages. Whether this affects the release of new thrombocytes from the bone marrow remains unclear.

As a whole there is little data about the clinically relevant half-life of ASA as an antiplatelet agent in neurosurgical patients. Park et al. [18] analyzed the amounts of blood drained and the indwelling times of drainage catheters in patients undergoing 1- or 2-level lumbar spinal fusion, comparing a control group not taking ASA to two groups of ASA users: One group that discontinued ASA 3 to 7 days and another that discontinued it 7 to 10 days prior to surgery. The group that stopped ASA 3 to 7 days prior to surgery had more blood drainage and longer catheter indwelling times, suggesting that the clinical effect of ASA as an antiplatelet agent might last at least 7 days. On the other hand, in a preliminary study by Gulpinar et al. [19] on 80 patients undergoing mostly abdominal procedures and in which platelet function was assessed by a platelet aggregation test comparable to the PFA-100® test, reducing the ASA-free period from 7 to 10 days to 4 to 5 days did not increase the risk of perioperative bleeding complications. Lee et al. [20] studied the recovery time of platelet function after aspirin withdrawal using multiple electrode aggregometry. Three days after the last ASA intake, the platelet activity gradually reached a point near the value of the controls, and there was no difference after more than 4 days when compared with the control group.

Thus, as already analyzed in the introduction, a review of the literature neither definitively answers the question of whether ASA needs to be stopped prior to neurosurgical procedures nor, if the answer is yes, does it indicate for precisely how long. However, the recovery time of platelet function after ASA withdrawal is stated to exhibit significant inter-individual variability. Therefore, the individual assessment of platelet function is considered a reasonable approach to put the patient at low risk and at the same time perform the operation as soon as possible.

In this regard, the most interesting subgroup of patients in our study was that of the patients on ASA admitted as emergencies but whose neurological conditions allowed surgery to be delayed until their platelet functions returned to normal. In most of these cases either the patients had spinal problems with immobilizing pain but no or only minor neurological deficits or they were in relatively good condition but had space-occupying chronic subdural hematomas that needed monitoring. Since platelet function returned to normal before the expected 7 days in 52 of these 86 patients, and even in only 0 to 3 days in 28, their preoperative hospital stays could be shortened significantly. In our study, the average time from last ASA administration to a normal test was 3.7 days as compared to the expected 7. As we didn't perform the PA test on a daily basis, the mean might be even shorter. Our data are matching those of Gulpinar et al. [19], suggesting that with individual testing preoperative ASA-free intervals can be reduced not only for abdominal but also for neurosurgical procedures. Our data also support those of Coma-Camella et al. [14], who found that ASA did not inhibit platelet function in 32% of patients taking it as an AA. Such patients could be identified with the PFA-100® test and were operated immediately, a very important benefit of the test especially in emergency situations. In contrast to the study of Kurak et al. [15], we did not find more intense bleeding in these patients, therefore supporting Coma-Camella's concept of a high percentage of ASA resistant patients instead of Kurak's suggestion that normal PA tests immediately after last ASA intake are merely a laboratory phenomenon.

Among our 40 scheduled patients who had discontinued ASA 7 days prior to admission, the test was of minor influence. Four patients had pathological PFA-100 tests at admission. In 2 of them, the test triggered a postponement of the operation although, according to the data of Akhavan-Sigari [5] and Cuellar [6], it is not clear whether this safety precaution was necessary. In the other 2 cases, however, the PAs indicated that these patients had additional, ASA-independent coagulation disorders, and both patients were treated conservatively.

In exceptional cases, the PA test was performed intraoperatively and led to a modification of the operative procedure and to the administration of special agents such as tranexamic acid. As these measures might have been indicated clinically even without the test, it is considered to be less relevant in such cases.

Normal PA results appeared to correlate well with the absence of intra- or postoperative bleeding complications. Since our patients with normal PAs had no major bleeding complications with surgery, we found the test to be a good indicator of adequate intraoperative

platelet function. On the other hand, bleeding complications occurred in 3 of 20 patients who underwent surgery despite pathological test results, but only in those with subdural hematomas and not in patients with spinal problems. Together with the data of Akhavan-Sighari [5], Cuellar [6], and Chen [9] mentioned above this supports our current assumption that discontinuing ASA might be more important in patients undergoing intracranial versus spinal surgery, although we have too few patients operated on while taking ASA to be statistically significant. Lillemäe et al. [10] conducted a recent observational study on the incidence of postoperative hematomas requiring surgical treatment in 8,783 neurosurgical patients and found an overall incidence of 0.6% after craniotomy, 1.1% after cervical and 2.1% after thoracolumbar spinal surgery. Based on these incidences, it is deemed impossible to obtain a number of patients sufficient for statistic relevance within a realistic time frame in our department only. A multicenter study would therefore be mandatory. While our data suggest that the test might be helpful in individually optimizing the timing of surgery when normal platelet function is considered a necessity, they leave open the question of which neurosurgical procedures might be performed in patients on ASA and for which procedures a normal platelet function is indeed mandatory.

A major limitation of the test was its lack of reliability in 12.3% of our patients with either low hematocrit and/or depressed platelet count. In such cases, the application of alternative, more complex thrombocyte aggregation tests, some of which are reliable down to a platelet count of 30/nanoliter, should be considered.

Conclusion

Since normal PFA-100 test results correlated well with uncomplicated surgery, the test may be a reliable tool for timing operations in neurosurgical patients admitted with ASA medication. As 87% of the patients needed fewer than the expected 7 days and 53% only 0 to 3 days to regain normal platelet function, the test could help in reducing preoperative delays for emergency patients. Main drawback of the method is the high rate of unreliable tests.

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