Impact of acetylsalicylic acid in patients undergoing cerebral aneurysm surgery – should the neurosurgeon really worry about it?

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Abstract
There has been an increase in the use of acetylsalicylic acid (ASA, Aspirin®) among patients with stroke and heart disease as well as in aging populations as a means of primary prevention. The potentially life-threatening consequences of a postoperative hemorrhagic complication after neurosurgical operative procedures are well known. In the present study, we evaluate the risk of continued ASA use as it relates to postoperative hemorrhage and cardiopulmonary complications in patients undergoing cerebral aneurysm surgery. We retrospectively analyzed 200 consecutive clipping procedures performed between 2008 and 2018. Two different statistical models were applied. The first model consisted of two groups: (1) group with No ASA impact - patients who either did not use ASA at all as well as those who had stopped their use of the ASA medication in time (> = 7 days prior to operation); (2) group with ASA impact - all patients whose ASA use was not stopped in time. The second model consisted of three groups: (1) No ASA use; (2) Stopped ASA use (> = 7 days prior to operation); (3) Continued ASA use (did not stop or did not stop in time, <7 days prior to operation). Data collection included demographic information, surgical parameters, aneurysm characteristics, and all hemorrhagic/thromboembolic complications. A postoperative hemorrhage was defined as relevant if a consecutive operation for hematoma removal was necessary. An ASA effect has been assumed in 32 out of 200 performed operations. A postoperative hemorrhage occurred in one out these 32 patients (3.1%). A postoperative hemorrhage in patients without ASA impact was detected and treated in 5 out of 168 patients (3.0%). The difference was statistically not significant in either model (ASA impact group vs. No ASA impact group: OR = 1.0516 [0.1187; 9.3132], p = 1.000; RR = 1.0015 [0.9360; 1.0716]). Cardiopulmonary complications were significantly more frequent in the group with ASA impact than in the group without ASA impact (p = 0.030). In this study continued ASA use was not associated with an increased risk of a postoperative hemorrhage. However, cardiopulmonary complications were significantly more frequent in the ASA impact group than in the No ASA impact group. Thus, ASA might relatively safely be continued in patients with increased cardiovascular risk and cases of emergency cerebrovascular surgery.

Keywords Acetylsalicylic acid · Aneurysm surgery · Clipping · Postoperative hemorrhage

Introduction
Low-dose Acetylsalicylic acid (ASA) is recommended as preventive treatment for many disorders, including coronary artery diseases (CAD) and stroke, as well as for patients receiving a percutaneous coronary or carotid artery stenting to prevent stent-thrombosis. In addition, many patients suffering from atrial fibrillation use aspirin or other anticoagulant therapies for prevention of stroke [5, 6, 8, 14, 18, 21, 27, 30, 37, 42, 43, 46, 48, 52].

By transfer of its acetyl group to serine residue in the platelet cyclooxygenase receptor ASA irreversibly inhibits platelet function. It prevents the configuration of thromboxane A2 and subsequently the aggregation of platelet for the entire lifecycle (7–10 days) [19, 20, 28, 31, 35, 41]. The inhibition of platelet function ensues even at lower dosages [10, 11, 44]. Abrupt interruption of ASA use may lead to a hypercoagulability, which are associated with some of the major adverse cardiovascular events that have been reported [33].
ASA has been proved as a major risk factor in the development of postoperative hemorrhage following neurosurgical procedures [36, 40]. Because postoperative rebleeding is frequently a life-threatening complication after intracranial operations, ASA is usually discontinued seven days or more prior to elective intracranial procedures [22, 28].

Weighting the risks of perioperative hemorrhage and cardiovascular complications of patients using ASA is a challenging task in daily neurosurgical routine. Yet, only a very limited number of studies evaluated the risk of ASA discontinuation or continuation before and after the neurosurgical treatment. There are a limited number of studies that have shown worse outcomes with pre-injury antiplatelet treatment [12, 16, 23, 24, 49]. However, a clear consensus on how to handle patients using ASA in the perioperative settings does not yet established [13, 17, 20, 25, 26, 32, 38, 47].

In the present study, we have evaluated the perioperative ASA management as it relates to the risk of postoperative hemorrhage and adverse cardiovascular events in patients undergoing neurosurgical treatment of ruptured and unruptured intracranial aneurysms.

Methods

This retrospective study analyzed the medical records of all consecutive patients who underwent clipping procedures at our institution between 2008 and 2018. All aneurysms were treated via “traditional” microsurgical clipping. In only one patient two aneurysm were sealed in one session. In all other SAH patients, the ruptured aneurysm only was clipped. Clinical data on patients were obtained by retrospective chart review, and included:

- age
- sex
- blood group
- body mass index (BMI)
- perioperative use of ASA
- hypertension
- smoking history
- laboratory parameters
- subarachnoid hemorrhage/unruptured aneurysm
- length of hospitalization
- Hunt and Hess scale
- Fisher Grade
- location and size of aneurysm
- multiplicity of aneurysms
- operative procedure
- op-duration
- blood loss
- complications (hemorrhage, deep vein thrombosis, etc.)
- peri- and postoperative Karnofsky performance status (KPS), Glasgow outcome score (GOS)

In 43 patients the data records revealed ASA in the recent medical history. Of these, 11 patients discontinued the ASA use timely prior to surgery. However, in 32 patients the ASA use was not stopped at all or timely. The common ASA dosage was 100 mg, except in three patients, were the ASA dosage was 250 mg, 500 mg and 1000 mg.

To test for possible ASA impact on postoperative hemorrhage two different statistical models utilizing Fisher’s exact test were applied. The first model consisted of two groups:

- No ASA impact - patients who either had not used ASA medication at all or who had stopped the use of ASA at or before the recommended time (> = 7 days prior to operation)
- ASA impact - all patients who had not discontinued ASA use within the recommended time frame

The second model consisted of three groups:

- No ASA use
- Stopped ASA use (> = 7 days prior to operation);
- Continued ASA use (did not stop use <7 days prior to operation or did not stop use at all).

A postoperative hemorrhage was defined as relevant if a subsequent operation for hematoma removal was necessary. Major thromboembolic complications were defined as myocardial infarction and/or pulmonary embolism.

Data storage and statistical analyses were performed using the software package SAS University Edition (SAS Institute, Inc., Cary, New York, USA). Because the present analysis was performed in an explorative sense, it was deliberately reviewed to the full level of significance. Each $p$ value <0.05 therefore represented a statistically significant result. For unadjusted analyses, Fisher’s exact test was applied for categorical variables, and the robust t test (Satterthwaite) was used for continuous variables, where variables with extreme deviation from normal distribution had been log transformed.

Results

In total, 200 clipping operations were performed between 2008 and 2018. In the current study, we considered the most important complication after clipping surgery and divided it into two categories: postoperative hemorrhagic events and thromboembolic events. We studied potential risk factors of hemorrhagic complications regardless of ASA status. We evaluated the effects of demographic characteristics, aneurysm characteristics, hospitalization, and surgical features.
Postoperative hemorrhagic and thromboembolic complications were observed in less than 3% of the operations. Figure 2 shows two representative cases of postoperative hemorrhage. A total of 6 patients suffered a postoperative hemorrhage. Of these, one patient had used ASA (Table 1). Table 2 shows that there is no significant difference in postoperative hemorrhage occurrence in the different groups. Re-craniotomy with evacuation of a hematoma was required no more frequently in the ASA impact group than in the No ASA impact group ($p = 1.0$). As also shown in Fig. 1 and Table 2, in the case of ASA use, there is also no significant difference in the risk of postoperative hemorrhage between the three conditions ($p = 0.835$).

Age and sex of patients and other demographic characteristics such as body mass index (BMI), blood group, hypertension and smoking history were nearly equally distributed. There was no significant difference in patient age between the No ASA impact group ($N = 168 / 55.6 ± 11.4$ years) and the ASA impact group ($N = 32 / 59.4 ± 14.0$ years) [$p = 0.150$]. These demographic characteristics are presented in Table 3 and do not impact on the postoperative hemorrhagic frequency in the different groups.

Clipping was performed in 148 cases on patients who suffered subarachnoid hemorrhage (SAH) and in 52 cases on patients who had unruptured intracranial aneurysms (UIA). Out of the 32 patients operated under the impact of ASA 24 suffered from SAH. Subsequent urgent operations prevented the timely withdrawal of ASA. In the remaining 8 patients, discontinuation of ASA would have resulted in an increased cardiovascular risk (e.g. following recent placement of coronary stents). There was no significant difference in distribution between the No ASA impact ($N = 124$ SAH vs. $N = 44$ UIA) and the ASA impact groups ($N = 24$ SAH vs. $N = 8$ UIA) [$p = 1.000$]. The classification according to the Hunt and Hess scale, the modified Fisher grade in patients with SAH, and the length of hospitalization in both groups, as well as any thrombosis prophylaxis, showed no significant difference between the No ASA impact and the ASA impact groups. However, there was a significant difference in length of hospitalization (Table 4) between patients without postoperative hemorrhage ($N = 194 / 15.6 ± 9.1$ days) and patients with postoperative hemorrhage ($N = 6 / 25.0 ± 8.7$ days) [$p = 0.045$].

With regard to a postoperative hemorrhage, aneurysm size proved to play a role and was the only statistically significant parameter ($N = 194$: $7.1 ± 4.6$ mm vs. $N = 6$: $4.7 ± 2.2$; $p = 0.042$). As shown in Table 5, all other analyzed aneurysm characteristics did not significantly correlate with the risk of postoperative hemorrhage.

Blood loss during surgery was similar for the No ASA impact group ($197.6 ± 46.5$ ml) and the ASA-impact group ($203.9 ± 40.5$ ml; $p = 0.438$). The other operative parameters (Table 6), such as duration of surgery and application of temporary clipping did not play a role in the occurrence of a postoperative hemorrhage. The perioperative laboratory parameters including international normalized ratio (INR), partial thromboplastin time (PTT) [sec], thrombin time (TT) [sec] and platelet count ($10^9/l$) showed no significant difference between the study groups.

### Table 1 – Demographic and aneurysm characteristics of patients suffered from postoperative hemorrhage

| # | Age [years] | Gender | SAH | ASA | Hemorrhage | Aneurysm |
|---|---|---|---|---|---|---|
| 1 | 78 | female | yes | 100 mg | intracerebral | ipsilateral MCA right | 3.4 |
| 2 | 57 | female | no | no | intracerebral | contralateral MCA right | 3.3 |
| 3 | 65 | female | yes | no | subdural | ipsilateral | 4 |
| 4 | 62 | female | no | no | subgaleal | ipsilateral | 9 |
| 5 | 45 | male | yes | no | epidural | ipsilateral MCA left | 3.6 |
| 6 | 63 | female | yes | no | intracerebral | ipsilateral MCA left | 5 |

### Table 2 – No evidence for increased risk from continued ASA use has been found

| ASA impact | ASA use | ASA dosage mean±SD [mg] | N (% column) | N (% row) | N (% row) | p value |
|---|---|---|---|---|---|---|
| No | No | 6.5±24.8 | 168 (84.0) | 163 (97.0) | 5 (3.0) | 1.000 |
| Yes | Yes | 145.3±172.9 | 32 (16.0) | 31 (96.9) | 1 (3.1) |
| Stopped | No | 0.0±0.0 | 157 (78.5) | 152 (96.8) | 5 (3.2) | 0.835 |
| Continued | Stopped | 100.0±0.0 | 11 (5.5) | 11 (100.0) | 0 (0.0) |
| Sum | Continued | 145.3±172.9 | 32 (16.0) | 31 (96.9) | 1 (3.1) |
| Sum | No | 200 | 194 (97.0) | 6 (3.0) |
Table 7 shows the frequency of cardiopulmonary complications of the investigated patients. Five patients suffered a pulmonary embolism after a deep vein thrombosis. One of these patients had not taken ASA. In one patient the ASA medication was discontinued in time. Three patients suffered pulmonary embolism under ASA impact. This type of complication was significantly more frequent in the ASA impact group than in the No ASA impact group (p = 0.030). However, the occurrence of cardiopulmonary complications was independent of whether ASA use had been discontinued or not been used at all prior to surgery.

Discussion

We investigated the impact of perioperative ASA treatment on postoperative hemorrhage, thromboembolic complications and clinical parameters in patients undergoing aneurysm-clipping operations for ruptured and unruptured intracranial aneurysms. In our study cohort, we could not observe that perioperative ASA use does result in increased hemorrhagic complications for aneurysm-clipping surgery.

In some studies, aneurysm characteristics such as size and posterior circulation location, as well as demographic characteristics such as patient age and case volume were seen as risk factors for surgical treatment of UIA [1–3, 34, 51, 53]. In our study, aneurysm size proved to be an independent risk factor indicating that smaller aneurysms are associated with an increased risk of postoperative hemorrhage. This observation is contrary to the findings by Nakamizo et al. [38], who did not observe an impact of aneurysm size on the rate of postoperative hemorrhage.

Nakamizo et al. [38] reveal in their study on patients undergoing craniotomy for UIA that intracranial hemorrhage was more frequent in the group that was receiving antithrombotic treatment than in the group not receiving antithrombotic drugs. In a study by Toyoda et al. [50] it was found that neither double treatment with antiplatelet inhibitors nor the addition of an antiplatelet inhibitor to
warfarin placed patients at increased risk of perioperative bleeding. An aggravated postoperative hemorrhage risk due to the intake of ASA could not be confirmed in our study. Hanalioglu et al. [20] demonstrated - similar to our study - that perioperative ASA use was not associated with an increased rate of hemorrhagic complications after intracranial tumor surgery. Unsurprisingly, we found a significant difference in length of hospitalization time between those patients with postoperative hemorrhage compared to patients without hemorrhage. It is relatable that for patients with postoperative hemorrhage, the recovery phase and thus the length of hospital stay is longer.

In our study, cardiopulmonary complications were significantly more frequent in the ASA impact group than in the No ASA impact group. Some studies suggest that discontinuing ASA medication in patients receiving antithrombotic treatment can pose a significant risk factor of both thromboembolic and bleeding events [4, 15]. The international, randomized, placebo-controlled trial (POISE-2) revealed that the perioperative use of ASA had no significant impact on mortality, but increased the risk of major hemorrhage [9]. Our results are somehow conflicting with the assumption of Gerstein et al. [15] who supposed that abrupt discontinuation of long-term ASA usage could lead to platelet rebound phenomena resulting in increased risk of thrombosis. The role of ASA (−withdraw) in the context of deep venous thrombosis and pulmonary embolism after SAH remains unclear. During the study period, postoperative thrombosis prophylaxis using low molecular weight heparin was not administrated routinely for cranial surgery, thus, based on our data reliable conclusions cannot be drawn [45]. For the prevention of venous thromboembolism most patients used compression stockings only.

Recent guidelines in anesthesiology and cardiology recommend perioperative ASA continuation in patients with low to moderate bleeding risk and high cardiovascular risk [7, 39]. Intracranial operations as well as intramedullary spinal surgeries are considered high-risk bleeding procedures and are therefore excluded from recommendations for ASA continuation, even in patients with a high cardiovascular risk [39]. A national survey of neurosurgeons in Germany studying the use of ASA prior to intracranial operations revealed that 77.5% of those responding believed that patients taking low-dose ASA had an increased risk of major perioperative

| Table 3 – Demographic characteristics of the investigated patients |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Operations      | No ASA impact   | ASA impact      | p value         | No hemorrhage   | Hemorrhage      | p value         |
|                | N (%) | N (%) / mean±SD | N (%) / mean±SD |                 | N (%) / mean±SD | N (%) / mean±SD |
| Demographic information |        |                 |                 |                 |                 |                 |
| Age [years]   | 200   | 168 / 55.6±11.4 | 32 / 59.4±14.0 | 0.150           | 194 / 56.0±11.9 | 6 / 61.7±10.8 | 0.259           |
| Gender        | 200   |                 |                 |                 |                 |                 |
| female        | 139 (69.5) | 117 (84.2) | 22 (15.8) | 1.000           | 134 (96.4) | 5 (3.6) | 0.669           |
| male          | 61 (30.5)  | 51 (83.6)   | 10 (16.4)  |               | 60 (98.4)   | 1 (1.6)   |               |
| Height [cm]   | 187   | 156 / 169.1±8.1 | 31 / 168.0±9.9 | 0.574           | 182 / 168.9±8.0 | 5 / 170.2±18.7 | 0.884           |
| Weight (kg)   | 187   | 156 / 74.2±14.1 | 31 / 75.5±14.0 | 0.638           | 182 / 74.3±14.1 | 5 / 77.4±14.6 | 0.665           |
| Body mass index | 187   | 156 / 25.9±4.6 | 31 / 26.7±4.5 | 0.355           | 182 / 26.0±4.6 | 5 / 26.9±4.5 | 0.690           |
| Blood group (AB0) | 180   | 71 (39.4) | 60 (84.5) | 11 (15.5) | 0.483           | 71 (100.0) | 0 (0.0) | 0.100           |
| A              | 71 (39.4) | 60 (84.5) | 11 (15.5) | 0.483           | 71 (100.0) | 0 (0.0) | 0.100           |
| B              | 25 (13.9) | 23 (92.0) | 2 (8.0)   |               | 24 (96.0)   | 1 (4.0)   |               |
| AB             | 9 (5.0)   | 8 (88.9)   | 1 (11.1)  |               | 8 (88.9)    | 1 (11.1)  |               |
| 0              | 75 (41.7) | 59 (78.7) | 16 (21.3) |               | 72 (96.0)   | 3 (4.0)   |               |
| Blood group (rhesus) | 180   | 155 (86.1) | 126 (81.3) | 29 (18.7) | 0.083           | 151 (97.4) | 4 (2.6) | 0.531           |
| Rh+            | 155 (86.1) | 126 (81.3) | 29 (18.7) | 0.083           | 151 (97.4) | 4 (2.6) | 0.531           |
| Rh-            | 25 (13.9) | 24 (96.0) | 1 (4.0)   |               | 24 (96.0)   | 1 (4.0)   |               |
| Hypertension   | 200   | 89 (44.5) | 72 (80.9) | 17 (19.1) | 0.334           | 87 (97.8) | 2 (2.2) | 0.694           |
| Yes            | 89 (44.5) | 72 (80.9) | 17 (19.1) | 0.334           | 87 (97.8) | 2 (2.2) | 0.694           |
| No             | 111 (55.5) | 96 (85.6) | 15 (13.5) |               | 107 (96.4) | 4 (3.6) |               |
| Smoker         | 200   | 70 (35.0) | 58 (82.9) | 12 (17.1) | 0.840           | 68 (97.1) | 2 (2.9) | 1.000           |
| Yes            | 70 (35.0) | 58 (82.9) | 12 (17.1) | 0.840           | 68 (97.1) | 2 (2.9) | 1.000           |
| No             | 130 (65.0) | 110 (84.6) | 20 (15.4) |               | 126 (96.9) | 4 (3.1) |               |
### Table 4 – Clinical parameters. Unsurprisingly, patients with postoperative hemorrhaging spent a significantly longer time in hospital

| Operations          | No ASA impact | ASA impact | p value | No hemorrhage | Hemorrhage | p value |
|---------------------|---------------|------------|---------|---------------|------------|---------|
|                     | N (%)         | N (%) / mean±SD | N (%) / mean±SD | N (%) / mean±SD | N (%) / mean±SD | N (%) / mean±SD |
| **Hospitalization/SAH** |               |            |         |               |            |         |
| Duration [days]     | 200           | 168 / 15.9±9.5 | 32 / 16.2±7.7 | 0.845         | 194 / 15.6±9.1 | 6 / 25.0±8.7 | 0.045 |
| Subarachnoid hemorrhage | 200          |             |         |               |            |         |
| Yes                 | 148 (74.0)    | 124 (83.8)  | 24 (16.2) | 1.000         | 144 (97.3) | 4 (2.7)  | 0.651 |
| No                  | 52 (26.0)     | 44 (84.6)   | 8 (15.4)  | 50 (96.1)     | 2 (3.9)    |           |       |
| Hunt and Hess scale | 138           |             |         |               |            |         |
| 1                   | 42 (30.4)     | 35 (83.3)   | 7 (16.7)  | 0.407         | 40 (95.2)  | 2 (4.8)  | 0.296 |
| 2                   | 24 (17.4)     | 22 (91.7)   | 2 (8.3)   | 22 (91.7)     | 2 (8.3)    |           |       |
| 3                   | 17 (12.3)     | 12 (70.6)   | 5 (29.4)  | 17 (100.0)    | 0 (0.0)    |           |       |
| 4                   | 43 (31.2)     | 35 (81.4)   | 8 (18.6)  | 43 (100)      | 0 (0.0)    |           |       |
| 5                   | 12 (8.7)      | 11 (91.7)   | 5 (8.3)   | 12 (100.0)    | 0 (0.0)    |           |       |
| Fisher grade (modified) | 137       |             |         |               |            |         |
| 0                   | 2 (1.5)       | 2 (100.0)   | 0 (0.0)   | 0.649         | 2 (100.0)  | 0 (0.0)  | 0.305 |
| 1                   | 4 (3.0)       | 4 (100.0)   | 0 (0.0)   | 4 (100.0)     | 0 (0.0)    |           |       |
| 2                   | 21 (15.3)     | 18 (85.7)   | 3 (14.3)  | 20 (95.2)     | 1 (4.8)    |           |       |
| 3                   | 53 (38.7)     | 46 (86.8)   | 7 (13.2)  | 50 (94.3)     | 3 (5.7)    |           |       |
| 4                   | 57 (41.6)     | 44 (77.2)   | 13 (22.8) | 57 (100.0)    | 0 (0.0)    |           |       |
| **Thromboprophylaxis** | 188         |             |         |               |            |         |
| No                  | 176 (93.6)    | 149 (84.7)  | 27 (15.3) | 0.411         | 170 (96.6) | 6 (3.4)  | 1.000 |
| Yes                 | 12 (6.4)      | 9 (75.0)    | 3 (25.0)  | 12 (100.0)    | 0 (0.0)    |           |       |

### Table 5 – Aneurysm characteristics. The size of the aneurysm might be a factor influencing the risk of postoperative hemorrhage

| Operations          | No ASA impact | ASA impact | p value | No hemorrhage | Hemorrhage | p value |
|---------------------|---------------|------------|---------|---------------|------------|---------|
|                     | N (%)         | N (%) / mean±SD | N (%) / mean±SD | N (%) / mean±SD | N (%) / mean±SD | N (%) / mean±SD |
| **Aneurysm characteristics** |               |            |         |               |            |         |
| Aneurysm location   | 200           |             |         |               |            |         |
| MCA                 | 134 (67.0)    | 109 (81.3)  | 25 (18.7) | 0.155         | 128 (95.5) | 6 (4.5)  | 0.874 |
| Acom                | 31 (15.5)     | 29 (93.6)   | 2 (6.4)  | 31 (100.0)    | 0 (0.0)    |           |       |
| ACA                 | 16 (8.0)      | 15 (93.7)   | 1 (6.3)  | 16 (100.0)    | 0 (0.0)    |           |       |
| ACI                 | 12 (6.0)      | 10 (83.3)   | 2 (16.7) | 12 (100.0)    | 0 (0.0)    |           |       |
| PICA                | 3 (1.5)       | 1 (33.3)    | 2 (66.7) | 3 (100.0)     | 0 (0.0)    |           |       |
| Pcom                | 2 (1.0)       | 2 (100.0)   | 0 (0.0)  | 2 (100.0)     | 0 (0.0)    |           |       |
| VA                  | 2 (1.0)       | 2 (100.0)   | 0 (0.0)  | 2 (100.0)     | 0 (0.0)    |           |       |
| Circulation         | 200           |             |         |               |            |         |
| Anterior            | 195 (97.5)    | 165 (84.6)  | 30 (15.4) | 0.012         | 189 (96.9) | 6 (3.1)  | 1.000 |
| Posterior           | 5 (2.5)       | 3 (60.0)    | 2 (40.0) | 5 (100.0)     | 0 (0.0)    |           |       |
| Hemisphere          | 200           |             |         |               |            |         |
| Right               | 115 (57.5)    | 97 (84.3)   | 18 (15.7) | 1.000         | 112 (97.4) | 3 (2.6)  | 0.788 |
| Left                | 85 (42.5)     | 71 (83.5)   | 14 (16.5) | 82 (96.5)     | 3 (3.5)    |           |       |
| Size [mm]           | 200           | 168 / 7.1±4.6 | 32 / 7.0±4.0 | 0.992         | 194 (7.1±4.6) | 6 (4.7±2.2) | 0.042 |
| Number of aneurysms |               |            |         |               |            |         |
| Single              | 128 (64.0)    | 110 (85.9)  | 18 (14.1) | 0.323         | 122 (95.3) | 6 (4.7)  | 0.089 |
| Multiple            | 72 (36.0)     | 58 (80.6)   | 14 (19.4) | 72 (100.0)    | 0 (0.0)    |           |       |
| Shape of aneurysm   | 200           |             |         |               |            |         |
| Saccular            | 144 (72.0)    | 118 (81.9)  | 26 (18.1) | 0.283         | 142 (98.6) | 2 (1.4)  | 0.053 |
| Multilobar          | 56 (28.0)     | 50 (89.3)   | 6 (10.7)  | 52 (92.9)     | 4 (7.1)    |           |       |

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hemorrhage [28]. Of those respondents, 58% reported personal experience with perioperative bleeding. The same group also reported the results of a study on spinal surgery that found a similar percentage of perioperative bleeding occurrence. Nevertheless, in a related study only a small fraction (5%) of neurosurgeons would agree to perform spinal surgery under ASA medication [29].

However, some limiting aspects beyond the obvious flaws of retrospective study designs have to be discussed. In the reported period functional platelet testing was not available in time for most patients. Therefore, statistical analysis was not feasible and reliable conclusions regarding ASA non-responder were not possible. Furthermore, the treatment strategies were different in several cases, particularly in patients with multiple aneurysms. However, due to the relatively low incidence of posthemorrhagic events subgroup analysis were not useful.

### Table 6

| Operations | No ASA impact | ASA impact | p value | No hemorrhage | Hemorrhage | p value |
|------------|---------------|------------|---------|---------------|------------|---------|
| N (%)      | N (%) / mean±SD | N (%) / mean±SD |         | N (%) / mean±SD | N (%) / mean±SD |
| Operation time [min] | 200 | 168 / 197.6±46.5 | 32 / 203.9±40.5 | 0.438 | 194 / 198.6±46.0 | 6 / 197.7±27.0 | 0.938 |
| Temporary clipping (sec) | 48 | 37 / 143.2±125.6 | 11 / 245.4±165.6 | 0.080 | 46 / 164.5±141.8 | 2 / 215.5±142.1 | 0.701 |
| Blood loss (ml) | 185 | 154 / 365.2±341 | 31 / 348.5±220.5 | 0.730 | 180 / 367.4±327.0 | 5 / 282.6±138.9 | 0.270 |

### Laboratory parameters

- **International normalized ratio (INR)**
  - N (%) | N (%) / mean±SD | N (%) / mean±SD | p value |
  - 173 | 144 / 1.0±0.1 | 29 / 1.0±0.1 | 0.852 |
  - 173 | 168 / 27.9±2.5 | 6 / 28.0±2.4 | 1.000 |

- **Partial thromboplastin time (PTT) [sec]**
  - N (%) | N (%) / mean±SD | N (%) / mean±SD | p value |
  - 200 | 168 / 27.5±3.0 | 32 / 27.5±3.0 | 0.383 |
  - 200 | 166 / 15.9±2.1 | 31 / 15.9±2.1 | 0.701 |

- **Thrombin time (TT) [sec]**
  - N (%) | N (%) / mean±SD | N (%) / mean±SD | p value |
  - 192 | 168 / 90.7±16.1 | 32 / 90.7±16.1 | 0.289 |
  - 192 | 156 / 90.7±16.1 | 29 / 90.7±16.1 | 0.829 |

- **Platelet count (10^9/l)**
  - N (%) | N (%) / mean±SD | N (%) / mean±SD | p value |
  - 200 | 168 / 261.8±85.3 | 32 / 280.4±90.7 | 0.289 |
  - 200 | 156 / 266.0±87.0 | 29 / 225.8±45.7 | 0.148 |

### Performance status/Outcome

- **KPS postoperative**
  - N (%) | N (%) / mean±SD | N (%) / mean±SD | p value |
  - 199 | 168 / 72.3±28.0 | 31 / 64.8±3.2 | 0.245 |
  - 199 | 193 / 71.5±29.0 | 6 / 60.0±26.1 | 0.334 |

- **Glasgow outcome score (GOS)**
  - N (%) | N (%) / mean±SD | N (%) / mean±SD | p value |
  - 199 | 168 / 4.2±1.1 | 31 / 3.7±1.4 | 0.095 |
  - 199 | 193 / 4.1±1.2 | 6 / 4.0±1.3 | 0.843 |

### Table 7

Cardiopulmonary complications were significantly more frequent in the **ASA-impact** group than in the **No-ASA-impact** group. However, a short-term discontinuation of ASA treatment seems to have had no influence on the incidence of perioperative thromboembolic complications.

| ASA impact | Cardiopulmonary complications | p value |
|------------|-----------------------------|---------|
| No | | 0.030 |
| Yes | | 0.009 |
| Stopped | | 1.000 |
| Continued | | 0.843 |

### Conclusion

In this study continued ASA use was not associated with an increased risk of a postoperative hemorrhage in patients undergoing aneurysm surgery. In contrast, cardiopulmonary complications were significantly more frequent in the **ASA-impact** group than in the **No-ASA-impact** group. However, in patients with increased cardiovascular risk and in the case of emergency surgery, ASA might relatively safe be continued. Aneurysms size was found to be an independent risk factor regarding the incidence of postoperative hemorrhage. Prospective randomized studies are necessary to evaluate the risks and safety of the perioperative use of ASA in neurosurgical procedures with respect to epidemiological changes and increased use of antiplatelet treatment or anticoagulation.
Authors' contributions Conceptualization: Ali Rashidi, Michael Luchtmann.

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Ethics approval and consent to participate The presented study was conducted in compliance with the national legislation and the code of ethical principles for medical research involving human subjects of the world medical association (Declaration of Helsinki). The collection, analysis and publication of retrospective clinical data is generally approved by the ethics committee of the Medical Faculty of the Otto-von-Guericke University of Magdeburg. The study was approved and registered by the institutional review board (IRB) of the Medical Faculty of the Otto-von-Guericke University of Magdeburg (Register#: R0320). Necessity for patient’s informed consent was waived by the IRB.

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Code availability Not applicable.

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References

1. Alshekhlee A, Mehta S, Edgell RC, Vora N, Feen E, Mohammadi A, Kale SP, Cruz-Flor S (2010) Hospital mortality and complications of electively clipped or coiled unruptured intracranial aneurysms. Stroke 41:1471–1476. https://doi.org/10.1161/strokeaha.110.580647

2. Barker FG 2nd, Amin-Hanjani S, Butler WE, Hoh BL, Rabinov JD, Pryor JC, Ogilvy CS, Carter BS (2004) Age-dependent differences in short-term outcome after surgical or endovascular treatment of unruptured intracranial aneurysms in the United States, 1996-2000. Neurosurgery 54:18–28; discussion 28-30. https://doi.org/10.1227/01.neu.0000097195.48840.c4

3. Brinjikji W, Rabinstein AA, Lanzino G, Kallmes DF, Cloft HJ (2011) Effect of age on outcomes of treatment of unruptured cerebral aneurysms: a study of the National Inpatient Sample 2001-2008. Stroke 42:1320–1324. https://doi.org/10.1161/strokeaha.110.607986

4. Burger W, Chemnittius JM, Kneissl GD, Rucker G (2005) Low-dose aspirin for secondary cardiovascular prevention - cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation - review and meta-analysis. J Intern Med 257:399–414. https://doi.org/10.1111/j.1365-2796.2005.01473.x

5. Cohen AT, Imfeld S, Markham J, Granziol S (2015) The use of aspirin for primary and secondary prevention in venous thromboembolism and other cardiovascular disorders. Thromb Res 135:217–225. https://doi.org/10.1016/j.thromres.2014.11.036

6. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients (2002). BMJ (Clinical research ed) 324:71–86. doi:https://doi.org/10.1136/bmj.324.7329.71

7. Darvish-Kazem S, Douketis JD (2012) Perioperative management of patients having noncardiac surgery who are receiving anticoagulant or antiplatelet therapy: an evidence-based but practical approach. Semin Thromb Hemost 38:652–660. https://doi.org/10.1055/s-0032-1326781

8. de Gaetano G (2001) Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. Lancet (London, England) 357:89-95. https://doi.org/10.1016/s0140-6736(00)03539-x

9. Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, Villar JC, Sigamani A, Biccard BM, Meyhoff CS, Parlow JL, Guyatt G, Robinson A, Garg AX, Rodsenth RN, Botto F, Lurati Buse G, Xavier D, Chan MT, Tiboni M, Cook D, Kumar PA, Forget P, Malaga G, Fleischmann E, Amir M, Eikelboom J, Mizera R, Torres D, Wang CY, VanHelder T, Paniagua P, Berwanger O, Srinathana S, Graham M, Pasin L, Le Manach Y, Gao P, Pogue J, Whittlock R, Lamy A, Kearon C, Baigent C, Chow C, Pettit S, Chrolavicius S, Yusuf S (2014) Aspirin in patients undergoing noncardiac surgery. N Engl J Med 370:1494–1503. https://doi.org/10.1056/NEJMoa1401105

10. Doutrémepuich C, de Seze JJ, Le Roy D, Lalanne MC, Anne MC (2010) Thrombectomy and publication of retrospective clinical data is generally approved by the ethics committee of the Medical Faculty of the Otto-von-Guericke University of Magdeburg. The study was approved and registered by the institutional review board (IRB) of the Medical Faculty of the Otto-von-Guericke University of Magdeburg (Register#: R0320). Necessity for patient’s informed consent was waived by the IRB.

11. Epp K, Nolte H (1993) Prolongation and normalization of bleeding time, platelet aggregation and coagulation. Haemostasis 20:99–105. https://doi.org/10.1159/000216114

12. Fabbri A, Servadei F, Marchesini G, Stein SC, Vandelli A (2010) Predicting intracranial lesions by antiplatelet agents in subjects with mild head injury. J Neurol Neurosurg Psychiatry 81:1275–1279. https://doi.org/10.1136/jnnp.2009.197467

13. Forster MT, Mathe AK, Senft C, Scharrer I, Seifert V, Gerlach R (2010) The influence of preoperative anticoagulation on outcome
and quality of life after surgical treatment of chronic subdural hematoma. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 17:975–979. https://doi.org/10.1016/j.jocn.2009.11.023
14. Gage BF, van Walraven C, Pearce L, Hart RG, Koudstaal PJ, Boode BS, Petersen P (2004) Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. Circulation 110:2287–2292. https://doi.org/10.1161/01.cir.0000145172.55640.93
15. Gerstein NS, Schulum PM, Gerstein WH, Petersen TR, Tawil I (2012) Should more patients continue aspirin therapy perioperatively?: clinical impact of aspirin withdrawal syndrome. Annu Surg 255:811–819. https://doi.org/10.1016/j.sla.0801318250054e
16. Grandhi R, Harrison G, Voronovich Z, Bauer J, Chen SH, Nicholas D, Alarcon LH, Okonkwo DO (2015) Preinjury warfarin, but not antiplatelet medications, increases mortality in elderly traumatic brain injury patients. The journal of trauma and acute care surgery 78:614–621. https://doi.org/10.1097/ta.0000000000000542
17. Guha D, Coyne S, Macdonald RL (2016) Timing of the resumption of antithrombotic agents following surgical evacuation of chronic subdural hematoma: a retrospective cohort study. J Neurosurg 124:750–759. https://doi.org/10.1093/jneurol/124.4.750
18. Guyatt GH, Akl EA, Guterman DD, Schuunemann HJ (2012) Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141:7s-47s. https://doi.org/10.1378/chest.1412S3
19. Hall R, Mazer CD (2011) Antiplatelet drugs: a review of their pharmacology and management in the perioperative period. Anesth Analg 112:292–318. https://doi.org/10.1213/ANE.0b013e318230f38d
20. Hanalioglu S, Sahin B, Sahin OS, Kozan A, Ucer M, Cikla U, Goodman SL, Baskaya MK (2019) Effect of perioperative aspirin use on hemorrhagic complications in elective craniotomy for brain tumors: results of a single-center, retrospective cohort study. J Neurosurg 132:1–10. https://doi.org/10.1093/jneurol/132.1.1
21. Hayden M, Pignone M, Phillips C, Mulrow C (2002) Aspirin in the perioperative period: a meta-analysis and side effects: the seventh ACCP conference on antithrombotic and antiplatelet drugs: the relationships among dose, effectiveness, and side effects: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 126:234s–264s. https://doi.org/10.1378/chest.126.3_suppl.234S
42. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WM, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germaino G, Hobbs R, Hoeks A, Karadeniz S, Mezzani A, Presti E, Ryden L, Scherer M, Syvanne M, Op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F (2012) European guidelines on cardiovascular disease prevention in clinical practice (version 2012): the fifth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). International journal of behavioral medicine 19:403–488. doi:https://doi.org/10.1007/s12529-012-9242-5, European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (Version 2012)

43. Pignone M, Alberts MJ, Colwell JA, Cushman M, Inzucchi SE, Mukherjee D, Rosenson RS, Williams CD, Wilson PW, Kirkman MS (2010) Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. Diabetes Care 33:1395–1402. https://doi.org/10.2337/dc10-0555

44. Powner DJ, Hartwell EA, Hoots WK (2005) Counteracting the effects of anticoagulants and antiplatelet agents during neurosurgical emergencies. Neurosurgery 57:823–831; discussion 823–831. https://doi.org/10.1227/01.neu.0000179915.74429.b2

45. Rachinger JC, Koman G, Scheller C, Prell J, Rampp S, Strauss C (2011) Practice in the perioperative prevention of deep vein thrombosis in German neurosurgical departments: is there a trend towards homogenization? Cent Eur Neurosurg 72:115–119. https://doi.org/10.1055/s-0031-1280791

46. Schomig A, Neumann FJ, Kastrati A, Schuhlen H, Blasini R, Hadamitzky M, Walter H, Zitzmann-Roth EM, Richardt G, Alt E, Schmitt C, Ulm K (1996) A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 334:1084–1089. https://doi.org/10.1056/nejm1996042533431702

47. Soleman J, Kamenova M, Guzman R, Mariani L (2017) The Management of Patients with chronic subdural hematoma treated with low-dose acetylsalicylic acid: an international survey of practice. World neurosurgery 107:778–788. https://doi.org/10.1016/j.wneu.2017.08.065

48. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, Topol EJ (2002) Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. Jama 288:2411–2420. https://doi.org/10.1001/jama.288.19.2411

49. Sumiyoshi K, Hayakawa T, Yatsushige H, Shigeta K, Momose T, Enomoto M, Sato S, Takasato Y (2017) Outcome of traumatic brain injury in patients on antiplatelet agents: a retrospective 20-year observational study in a single neurosurgery unit. Brain Inj 31:1445–1454. https://doi.org/10.1080/02699052.2017.1377349

50. Toyoda K, Iwasaki K, Nagata K, Koretsune Y, Sakamoto T, Uchiyama S, Gotoh J, Nagao T, Yamamoto M, Takahashi JC, Minematsu K (2008) Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: a prospective, multicenter, observational study. Stroke 39:1740–1745. https://doi.org/10.1161/strokeaha.107.504993

51. Wiebers DO, Whisnant JP, Huston J 3rd, Meissner I, Brown RD Jr, Piepras DG, Forbes GS, Thielen K, Nichols D, O’Fallon WM, Peacock J, Jaeger L, Kassell NF, Kongable-Beckman GL, Torner JC (2003) Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet (London, England) 362:103-110. https://doi.org/10.1016/s0140-6736(03)13860-3

52. Wolff T, Miller T, Ko S (2009) Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. preventive services task force. Ann Intern Med 150:405–410. https://doi.org/10.7326/0003-4819-150-6-200903170-00009

53. Zacharia BE, Bruce SS, Carpenter AM, Hickman ZL, Vaughan KA, Richards C, Gold WE, Lu J, Appelboom G, Solomon RA, Connolly ES (2014) Variability in outcome after elective cerebral aneurysm repair in high-volume academic medical centers. Stroke 45:1447–1452. https://doi.org/10.1161/strokeaha.113.004412

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